Membrane Biology

© Springer-Verlag New York Inc. 1993

# Topical Review

# Structure/Function Studies of the Epithelial Isoforms of the Mammalian Na<sup>+</sup>/H<sup>+</sup> Exchanger Gene Family

Ming Tse<sup>1</sup>, Sue Levine<sup>1</sup>, Chris Yun<sup>1</sup>, Steve Brant<sup>1</sup>, Laurent T. Counillon<sup>2</sup>, Jacques Pouyssegur<sup>2</sup>, Mark Donowitz<sup>1</sup>

<sup>1</sup>Departments of Medicine and Physiology, GI Unit, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Received: 3 March 1993/Revised: 27 April 1993

#### Introduction

Na<sup>+</sup>/H<sup>+</sup> exchangers or antiporters are plasma membrane transport proteins, which in eukaryotes exchange extracellular Na<sup>+</sup> for intracellular H<sup>+</sup> with a stoichiometry of 1:1 [31, 56]. In intact cells, Na<sup>+</sup> enters down the Na-K-ATPase generated electrochemical Na<sup>+</sup> gradient. All eukaryotic cells studied have plasma membrane Na<sup>+</sup>/H<sup>+</sup> exchangers, including yeast, *Caenorhabditis elegans* and crustaceans [1, 37, 49]. Prokaryotes have functionally similar Na<sup>+</sup>/H<sup>+</sup> exchanger proteins which regulate the intracellular Na<sup>+</sup> ion concentration and pH [38, 60]. In contrast to eukaryotic Na<sup>+</sup>/H<sup>+</sup> exchangers, prokaryotic Na<sup>+</sup>/H<sup>+</sup> exchangers are electrogenic, exchanging two intracellular Na<sup>+</sup> for 1 H<sup>+</sup>; usually utilizing the intracellular H<sup>+</sup> ion electromotive force.

In eukaryotic cells, the plasma membrane Na<sup>+</sup>/H<sup>+</sup> exchangers have multiple functions, including pH homeostasis, volume regulation, cell proliferation, and transcellular Na<sup>+</sup> absorption [reviewed in 31]. In no cell is it the only mechanism for any one of these functions. For instance, multiple mechanisms of pH homeostasis are present in most eukaryotic cells including a Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger, a Na<sup>+</sup>-dependent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger and multiple mechanisms of H<sup>+</sup> extrusion [reviewed in 41], including the H-K-ATPase pump.

In this review, we will focus on recent advances

**Key words:** Epithelial Na<sup>+</sup> absorption — Gene family — Kinase regulation — Growth factors — Membrane protein

Correspondence to: M. Donowitz

in identification and in understanding the structure/ function relationships and regulation of the mammalian Na<sup>+</sup>/H<sup>+</sup> exchanger gene family. The existence of multiple isoforms of mammalian Na<sup>+</sup>/H<sup>+</sup> exchangers had been predicted on the basis of: (i) While all Na<sup>+</sup>/H<sup>+</sup> exchangers are inhibited by the diuretic amiloride, they have widely different sensitivities to inhibition by amiloride from cell type to cell type and even between Na<sup>+</sup>/H<sup>+</sup> exchangers on different plasma membrane domains (apical vs. basolateral in polarized epithelial cells) in the same cell. This has been recently reviewed by Clark and Limbird [16]. (ii) Protein kinases have different effects in regulating Na<sup>+</sup>/H<sup>+</sup> exchangers depending not only on cell type, but also on different plasma membrane domains in the same cell [2, 16, 18, 20, 21, 35, 79]. With regard to the latter, Table 1 summarizes the effects of hormones, growth factors and protein kinases on intestinal and renal epithelial cells in which Na<sup>+</sup>/H<sup>+</sup> exchangers are found on apical and/or basolateral surfaces. In most cases, apical membrane Na<sup>+</sup>/H<sup>+</sup> exchangers are inhibited by C kinase [16], which stimulates the basolateral membrane Na<sup>+</sup>/H<sup>+</sup> exchanger; cAMP inhibits both apical and basolateral membrane Na<sup>+</sup>/H<sup>+</sup> exchangers. However, there are multiple exceptions to these generalizations. (iii) While it has been documented that regulation of Na<sup>+</sup>/H<sup>+</sup> exchangers can occur by a mechanism that shifts the pK value for the intracellular H<sup>+</sup> of the exchangers, protein kinase regulation of some Na<sup>+</sup>/H<sup>+</sup> exchanger isoforms involves a mechanism that changes the  $V_{\text{max}}$  of Na<sup>+</sup>/H<sup>+</sup> exchange. Such a change in  $V_{\text{max}}$  may or may not be accompanied by a change in pH dependence of intracellular  $H^+$  [35, 48, 51, 66, 76]. (iv)  $Na^+/H^+$  ex-

<sup>&</sup>lt;sup>2</sup>Department of Biochemistry, University of Nice, Nice, France

Table 1. Short-term kinase regulation of apical and basolateral Na<sup>+</sup>/H<sup>+</sup> exchange in cultured intestinal or renal cell lines or intact intestinal or renal tissue

Cells/tissues	Apical Na <sup>+</sup> /H <sup>+</sup> exchangers	Regulators			Basolateral Na +/H+ exchangers	Regulators				
		Hormones/growth factors		Protein kinase		excitatigers	Hormones/grow factors	vth	Protein kir	ase
LLC-PK/PE20 [11-13]	Yes	Calcitonin Vasopressin Phorbol Ester Forskolin 8-Br-cAMP	<b>↓ ↓ ↓ ↓ ↓</b>	A-Kinase C-Kinase	<b>↓</b>	Yes	8-Br-cAMP Forskolin Phorbol Ester Vasopressin	↓ ↑ ↑	A-Kinase C-Kinase	 ↑
A6 Cells [10]	No					Yes	Vasopressin Phorbol Ester Forskolin	$\overset{\downarrow}{\downarrow}$	A-Kinase C-Kinase	$\downarrow \\ \downarrow$
OK Cells [35, 53]	Yes	PTH Ca <sup>2+</sup> Forskolin 8-Br-cAMP Phorbol Ester	↓ ? ↓ ↓	A-Kinase C-Kinase	↓ ↓	No				
MCT Cells [54]	Yes	PTH Forskolin 8-Br-cAMP Phorbol Ester	<b>↓ ↓ ↓ ↓</b>	A-Kinase C-Kinase	ţ	Yes	PTH Phorbol Ester 8-Br-cAMP	$\uparrow \\ \downarrow$	A-Kinase C-Kinase	<b>↓</b>
RKPC-2 Cells [55]	Yes	PTH 8-Br-cAMP Phorbol Ester	<b>↓</b>	A-Kinase C-Kinase	<b>†</b>	Yes	PTH Phorbol Ester	<b>↓</b>	A-Kinase C-Kinase	<b>↓</b>
Caco-2 Cells [79]	No					Yes	Phorbol Ester Forskolin 8-Br-cAMP	0 0 0		
Rabbit Kidney [34, 53, 81-83]	Yes	8-Br-cAMP Phorbol Ester	<b>↓</b>	A-Kinase C-Kinase	<b>↓</b>	Yes				
Rabbit Small Intestine [17, 22-24, 58]	Yes	Ca <sup>2+</sup> /Calmodulin Phorbol Ester Carbachol EGF	<b>↓ ↓ ↑</b>	A-Kinase C-Kinase CaM-Kinase Tyrosine Kinase	<b>↓ ↓ ↓ ↑</b>	Yes	Serotonin	?		
Rat Small Intestine or Colon [22, 64]	Yes	EGF cAMP Ca <sup>2+</sup>	$\mathop{\downarrow}\limits_{\downarrow}$							

changers have been shown to have multiple physiologic roles, making it difficult to understand how a single transport protein could carry out so many functions. (v) By genomic Southern blot analysis, we demonstrated that the housekeeping Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE1) cDNA can hybridize to other closely related but not identical genes under low stringency hybridization and washing conditions [75].

## Identification of Na<sup>+</sup>/H<sup>+</sup> Exchanger Gene Family

Molecular identification of the mammalian Na<sup>+</sup>/H<sup>+</sup> exchanger was pioneered by Pouyssegur, Sardet and co-workers who used genetic complementation [67, 69] with fibroblast cell lines that they had selected to lack all endogenous Na<sup>+</sup>/H<sup>+</sup> exchangers (the Chinese hamster lung fibroblast derived cell line PS120 and the mouse fibroblast derived cell line LAPI [29, 61]). Since then additional members of this gene family have been identified, including an isoform that ap-

pears to be predominantly expressed in epithelial tissues [74] and an isoform expressed only in intestine, kidney, and stomach [59, 73]. Because there is no information concerning the total number of members of this gene family, we have named them in order of their molecular identification as NHE1 (standing for Na<sup>+</sup>/H<sup>+</sup> exchanger), NHE2, etc. NHE1 is the isoform cloned initially by Pouyssegur et al. [69]; NHE2 is an isoform expressed predominantly in epithelia [74]; and NHE3 is the isoform expressed only in a subset of epithelia [59, 72]. The cloning, sequencing, and expression of several members of this gene family have been accomplished.

Existence of a gene family of mammalian Na<sup>+</sup>/H<sup>+</sup> exchangers was demonstrated by our group and by Orlowski and Shull by cloning—to date, four mammalian isoform Na<sup>+</sup>/H<sup>+</sup> exchangers (NHE1, NHE2, NHE3 and NHE4) have been cloned and sequenced [59, 69, 72, 74]. NHE1, NHE2 and NHE3, [69, 72, 74] but as yet not NHE4, have been shown to function as Na<sup>+</sup>/H<sup>+</sup> exchangers based on functional complementation in PS120 fi-

broblasts. Since NHE4 is structurally related, it will be discussed as if it were a Na<sup>+</sup>/H<sup>+</sup> exchanger, although without having identified function this cannot be certain. Although NHE1, NHE2 and NHE3 are all inhibited by amiloride and 5'-amino substituted analogues, they exhibit a wide range of sensitivities to these drugs [16]. Additional members of the mammalian gene family almost certainly remain to be identified. At the least, these include a hippocampal isoform which is totally amiloride resistant [63], and perhaps some renal/intestinal forms. For instance, the OK (Opossum Kidney) cell line has a brush border Na<sup>+</sup>/H<sup>+</sup> exchanger but appears not to have message for NHE1, NHE2 or NHE3 ([52]; J. Pouyssegur, H. Murer unpublished).

#### NHEs Are Independent Gene Products

NHEs are separate gene products as predicted from their primary structure, with differences being present throughout the entire amino acid sequence. There are as yet no examples of alternately spliced Na<sup>+</sup>/H<sup>+</sup> exchanger isoforms. NHE1 and NHE3 have been mapped to separate chromosomes. NHE1 has been localized to human chromosome 1 p35-p36.1 by in situ hybridization of the NHE1 cDNA [50]. Genetic polymorphisms to restriction enzymes TaqI and MspI yielded 2 alleles for each enzyme with an observed heterozygosity of 47% each in unrelated individuals [50]. The NHE3 gene has been physically mapped to the distal portion of chromosome 5p 15.3 [9]. Probing EcoR1 digested human genomic DNAs detected three polymorphic sites containing a total of nine alleles. The observed heterozygosity for the NHE3 locus in unrelated individuals was 71%. Genetic mapping placed human NHE3 at chromosome 5p15.3, making NHE3 the most telomeric gene yet identified on this chromosome [9].

# Tissue Distribution of Na<sup>+</sup>/H<sup>+</sup> Exchanger Message and Protein

Based on Northern analysis and ribonuclease protection assays, NHE1 message is present in nearly all mammalian cells. The only mammalian cells studied in which NHE1 message was not identified are the OK renal proximal tubule cell line and rat proximal tubule cortical segments  $S_1$  and  $S_2$  [42]. All of these cells are known to lack basolateral Na $^+/H^+$  exchangers.

NHE2, NHE3 and NHE4 are more restricted in message distribution. NHE2 message is present in kidney, intestine, adrenal gland and much less in trachea and skeletal muscle [74] (Fig. 1). The message is most expressed in the kidney medulla exceeding that in the kidney cortex. In the gastrointestinal tract the ascending colon has the most message followed by jejunum > ileum > duodenum > descending colon.

In rabbit, NHE3 message is found exclusively in kidney, intestine, and stomach [72] (Fig. 1). The most message is present in the kidney cortex, exceeding the medulla. The area of second-most message is the rabbit ascending colon which is approximately equal to the ileum > the jejunum. NHE3 message is not present in the duodenum or descending colon. Orlowski characterized NHE3 message in rat [59] and found it was most present in the proximal colon exceeding the proximal small intestine = cecum = distal colon > kidney > stomach > duodenum > heart and brain. NHE3 message distribution is found in tissues that have neutral NaCl absorption, which is present in rat distal colon but is absent from rabbit descending colon [reviewed in 22].

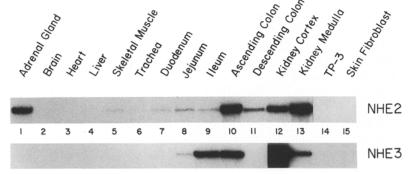
NHE4 message is present in largest amount in the rat stomach (maximum gastric antrum) > proximal small intestine = cecum = proximal colon with much smaller amounts in the uterus, brain, kidney, and skeletal muscle [59].

At the protein level, an antibody has only been used to localize NHE1. NHE1 is found in plasma membrane of fibroblasts. In the rabbit ileum it is restricted to the basolateral membrane of both the villus epithelial cell and the crypt epithelial cell, but appears to be diffusely present in the plasma membrane of goblet cells [75]. In addition, it is restricted to the basolateral membrane of the Cl<sup>-</sup> secretory human colon cancer cell line, Caco-2 [79]. It appears to be restricted to the basolateral membrane of the porcine renal epithelial cell line, LLC-PK1 as well [65]. In rabbit kidney, NHE1 is on the basolateral membrane of proximal tubule cells, distal convoluted tubules, thick ascending limb, and the collecting duct but is absent from glomeruli, and the thin descending loop of Henle [6].

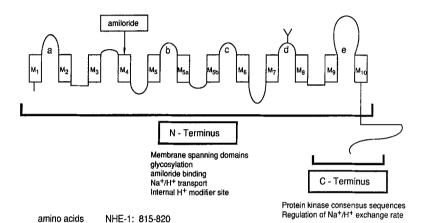
# Na<sup>+</sup>/H<sup>+</sup> Exchanger Gene Family—Structure

TOPOLOGY OF THE MAMMALIAN NHE GENE FAMILY

The primary structure (amino acids) and secondary structure (hydrophobicity profile) of all four identified mammalian Na<sup>+</sup>/H<sup>+</sup> exchanger gene family members are similar (Fig. 2). All isoforms appear to consist of a single type of subunit based on



**Fig. 1.** Ribonuclease protection assay demonstrating tissue distribution of message for NHE-2 above and NHE-3 below [reprinted from 72, 74].



**Fig. 2.** Topology predicted from hydrophobicity analysis of gene family of mammalian Na<sup>+</sup>/H<sup>+</sup> exchangers plus that determined by biochemical studies.

complementation of Na<sup>+</sup>/H<sup>+</sup> exchange activity by a single cDNA in an exchanger deficient cell [59, 69, 72, 74]. At least NHE1 appears to exist as a dimer structurally [26, 78] and dimerization might require disulfide linkage. It is not yet known whether the functional unit of NHE1 is a monomer or an oligomer. NHE1 has been cloned from human, rabbit, rat, pig (LLC-PK1 cells) and hamster ([19, 27, 36, 59, 65, 69, 71] and D. Pearse, personal communication); and contains 815–820 amino acids (species variation). NHE2 has been cloned from rabbit and has 809 amino acids [74]. NHE3 has been cloned from rat and rabbit and has 831 and 832 amino acids, respectively [59, 62]. NHE4 has been cloned from rat and has 717 amino acids [57]. The corresponding predicted sizes of NHE1, 2 and 3 based on amino acid composition as predicted from cDNAs without considering glycosylation are  $\sim 91$ ,  $\sim 91$ , and  $\sim 93$  kD, respectively, while the predicted size of NHE4 is ~81 kD.

NHE-2: 809

NHE-3: 831, 832

Figure 2 shows the predicted NHE topology. The molecule has two parts: an approximately 500 amino acid N-terminus and an approximately 300 amino acid C-terminus. As discussed below, these

two domains are involved in different functional aspects of Na<sup>+</sup>/H<sup>+</sup> exchange. Hydropathy analysis using the method of Engelman et al. [25] or Kyte and Doolittle [43] suggests that the N-terminus is made up of 10 or 12 membrane spanning  $\alpha$ -helices, respectively, and contains five extracellular hydrophilic loops (Fig. 2). Antibody studies indicate that the C-terminus for NHE1 is intracellular [69], based on the requirement for membrane permeabilization to visualize the epitope.

The most highly conserved portions of the molecule among the identified isoforms are the membrane spanning domains (Figs. 2, 4); and of these, membrane spanning domains 5A and 5B are the most conserved. Each protein is predicted to contain a signal peptide sequence at the N-terminus and the first membrane spanning domain may be cleaved off in the intact protein [28]. A single putative N-linked glycosylation consensus sequence is present in extracytoplasmic loop D in all isoforms [59, 69, 72, 74]. There are other putative N-linked glycosylation consensus sequences present in some isoforms which are not conserved, including one in the first extracytoplasmic loop in NHE1 [69]. The areas least

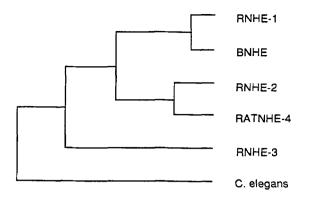


Fig. 3. Relationship among members of the eukaryotic  $Na^+/H^+$  exchanger gene family cloned to date based on amino acid identity using PC gene subprogram Clustal dendogram (R, rabbit; B, trout red blood cell; rat, rat).

related among the Na<sup>+</sup>/H<sup>+</sup> exchanger isoforms, include: (i) the first membrane spanning domain and extracellular loop A; and (ii) the intracytoplasmic C-terminal domain. There is even less relationship among the isoforms as the C-terminus is approached. The C-terminus for all isoforms contains multiple putative protein kinase consensus sequences. The individual putative protein kinase consensus sequences in the C-terminus are extremely variable among members of the gene family.

Based on comparison of the amino acid makeup of the individual NHE gene family members, NHE3 is the isoform which is most different from the others (Fig. 3). NHE2 and NHE4 most resemble each other. NHE1 is remarkably conserved across multiple species (human, rabbit, rat, hamster and pig), having at least 90% amino acid identity.

# NHE1 Is a Glycosylated Protein

Deglycosylation by neuraminidase and endoglycosidase F but not endoglycosidase H reduced the size of NHE1 from Mr 110,000 to 90,000 [65]. Thus NHE1 is N-glycosylated. NHE1 has two putative N-linked glycosylation consensus sequences in extracytoplasmic loops A and D [67]. It is not known whether both sites are glycosylated or whether glycosylation always is restricted to one and not the other. The functional consequences of deglycosylation of NHE1 are not yet described. although similar deglycosylation of rat renal brush border membranes with endoglycosidase F reduced the  $V_{\text{max}}$  of the Na<sup>+</sup>/H<sup>+</sup> exchanger without causing a change in the apparent  $K_m \text{Na}^+$  [86]. It is assumed but not yet demonstrated that NHE2, NHE3 and NHE4 are glycosylated.

# PHYLOGENETIC RELATIONSHIPS OF EUKARYOTIC NHEs

No detailed phylogenetic studies of Na<sup>+</sup>/H<sup>+</sup> exchangers have been carried out. In addition to the four mammalian isoforms, Na<sup>+</sup>/H<sup>+</sup> exchanger proteins have been identified at a molecular level in Escherichia coli [38, 60], the worm C, elegans [49], the yeast Schizosaccharomyces pombe [37], the trout [7], and multiple mammalian species including, to date, human, rat, rabbit, hamster and pig [19, 27, 59, 65, 71]. The E. coli Na<sup>+</sup>/H<sup>+</sup> exchanger physiologically acts to remove intracellular Na<sup>+</sup> in exchange for external H<sup>+</sup> using an intracellular alkaline pH gradient as the driving force. At least two E. coli exchangers have been identified [38, 60]. Neither appears to have significant homology with the eukaryotic Na<sup>+</sup>/H<sup>+</sup> exchangers at an amino acid level. They have 10-12 putative membrane spanning domains but a very short C-terminal domain and carry out electrogenic exchange of Na<sup>+</sup> and H<sup>+</sup>. The identified yeast Na<sup>+</sup>/H<sup>+</sup> exchanger has 12 putative membrane spanning domains, with four of the putative membrane domains having between 27 and 37% identity with the cloned mammalian exchangers (the most related portions of the molecule are the membrane spanning domains, 2, 5A, 5B and 10). The yeast exchanger also has some limited amiloride sensitivity. The yeast exchanger, however, does not have a long C-terminal domain as occurs in the mammalian exchangers. The C. elegans exchanger is much more closely related to mammalian Na<sup>+</sup>/H<sup>+</sup> exchangers in the partial clones so far obtained (Figs. 3, 4), having a similar hydrophobicity profile, 52% amino acid identity predominantly in the membrane spanning domains, and a cytoplasmic 220 amino acid C-terminus which contains several putative protein kinase consensus sequences. Thus, whereas the E. coli  $Na^+/H^+$  exchangers do not appear to be related to the eukaryotic isoforms, the yeast Na<sup>+</sup>/H<sup>+</sup> exchanger is related, although in a more primitive way, having some similarity in the transmembrane domains, while the C. elegans exchanger is a clearly related predecessor. Trout red blood cell Na<sup>+</sup>/H<sup>+</sup> exchanger has been cloned and shown to be closely related to NHE1 (it is also called B-NHE1 because of this similarity), but has differences in the C-terminus which allow cAMP to regulate its transport rate when expressed in PS120 cells [7].

#### **Functional Studies**

All cloned isoform Na<sup>+</sup>/H<sup>+</sup> exchangers functionally evaluated when expressed in fibroblasts (NHE1, NHE2 and NHE3) demonstrate an intracellular H<sup>+</sup>

MECHESCAP				
MCCSCAPT				
HRED  MESAUTORELETPEPT—LILLILLYU——CPAGALATLIAAPTLAAPTAMOTESS 48  BELEAN  MESAUTORELETPEPT—LILLILLYU——SASTYNES—SATTONTOCH 4  BELEAN  MESAUTORELETPEPT—LILLILLYU——SASTYNES—SATTONTOCH 4  BELEAN  MESAUTORELETPEPT—BERVANGVIERGHERRERAPTLATUTTEVPTEPTELSIJ 76  BELEAN  MESAUTORELETPETT—BERVANGVIERGHERRERAPTLATUTTEVPTEPTELSIJ 76  MESAUTORELETPETT 1	RNHE1	MLLWSAVRGLSPPPIVPSLLVVVALAGLLPGLRSHGLQLSPTDSTTPDSQPSRER		
ATTHER A  ### ### ### ### ### ### ### ### ###		MFSACTCRSLPTDDDDLLLLLLLLOVACDACALAFTILNADYAMCTCCC		
MSGROCC	RATNHE4			
SIGDVITAPPEVIP SERPWINGVIENDEMPREARPHIGIDITEVETPEISIA	RNHE3			
HITTITH	CELEGAN	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		
HITTITH		•		
PLEAD AND ADDITION OF PRINCIPAL CONTROL OF PRINCI	RNHE1	SIGDVTTAPPEVTPESRPVNRGVTEHGMKPRKAFPVLGIDYTHVRTPFEISLW	108	
ATTHESE AND ADDRESS OF THE PROPERTY OF THE PRO	BNHE	HLTNITNTHKAFPVLAVNYEHVRKPFEIALW	76	
HREEL  HOLD HALLIANGUE STATE PRODUCTION OF THE STATE OF THE STATE	RNHE2		87	
HELDAM HIT HALAMANIC PROPRIETIS LYPESCLLIVVELLVEGILEGYDER - PPFLOSTYF 150 HIT HALAMANIC PROPRIPTIS LYPESCLLIVVELLVEGILEGYDER - PPFLOSTYF 151 HIT HALAMANIC LYPESCH - PPFLOSTYF 151 HIT HALAMANI		RFAASSSDPDERISVFELDYDYVQIPYEVTLW		
HILLACIMALOFRUPTISSIVPESCLLIVVOLLVOGILIKOVGE-PPPLOSEVFF				
TILACIMICEPTUTFISSIVPESSILIVUSILINOTES-PPP1095FFF   102	CELEGAN		0	
TILACIMATOPPUTPTSSIVPESSLIVPULDVGITVOTES-PPT-DSGUFF   102		• • • • • • • • • • • • • • • • • • • •		
HREE    ILLALIMACEPPLIPRICATIVESCLIATIVE CLIVTCELE - PPVLOSQUFF   120				
THE ALLASIANICSHLYHDIPTYSSCALINVOLLOGIFOYDESSPANKTÖYFF 142  ATTRIBLE LICLASIANICSHLYHDIPTARDESCLILIVALAVASITUTHERSSPYMOSSIYF 111  ELEBAN				
LILASIANIGHLYBILPHESSCLIIVOALVOSITSTTBHESPYDOSSITY 115  BLEGON WHIRE CIRROPS LILVOALVOSITSTTBHESPYDOSSITY 115  BLEGON WHIRE CIRROPS LILVOALVOSITSTTBHESPYDOSSITY 146  WHIRE LILPFILDA-GYPTPERS LILVOALVOSITSTTBHESPYDOSITY 146  BELELPFILDA-GYPTPERS LILVOALVOSITSTBHESPYDOSITY 146  BELELPFILDA-GYPTPERS LILVOALVOSITSTBHESPYDOSITSTBHESP				
VLVASLARIYSHLSHVTSVVPSSALLTULGLIGUTUAGUTLAGUTATTTTTF 115  LEGGAN				
HEEDAM	NHE3			
HALE LELEPTILDA-GYFIPLRGYTERVOTILYRAYGINAFPIGGINYAVCLYGG HREE LCLEPTILDA-GYFIPLRGYTERVOTILYRAYGINAFPIGGINYAVCLYGG HREE LCLEPTILDA-GYFIPRFFFFFRANTIFYRAVOTIANAFPIGGINYAVCLYGG ATWREE LYLLPFYLUS-GYFIPRFFFFFRANTIFYRAVOTIANAFPIGGISLIANACGES ATWREE LYLLPFYLUS-GYFIPRFFFFFRANTIFYRAVOTIANAFFIGGSLIANACGES ATWREE LYLLPFILGSGYFFRANTIFYRAGSILANACGALALINAFTIGGSLIANAGTOL  SELEGAN LYLLPFILGSGYFFRANTIFYRAGSILANACGALALINAFTIGGSLIANAGTOL  SELEGAN LYLLPFILGSGYFFRANTIFYRALFERFRANTIFYRAVOTIANAFTIGGSLIANAGTOL  SELEGAN HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSSLIANATY 271 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSSLIANATY 272 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSSLIANATY 273 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 274 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 275 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 276 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 277 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 278 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 279 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 270 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 270 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 270 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 270 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 271 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 272 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 273 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 274 HREE LOTINGLIDALIFGSILSAVOFVAVIAVFEENHINGLIANITYGSILANATY 275 HREE HREE HREE HREE HREE HREE HREE HRE	ELEGAN			
HELD LILPFILDA-GYFIPLAGFENDGTILFAVOTUNGAFFENGGINTACLOG  HE LILPFILDA-GYFIPLAGFENGGINFAVOTUNGATGGINAFFENGGINTACLOGIS  ANNISA LILPFIVLDA-GYFIPPENGGINFAVOTUNGATGGINAFFENGGINTACLOGIS  HELDA-GYFIPPENGGINFANGGINFAVOTUNGATGGINFACTOR  HELDA-GYFIPPENGGINFANGGINFANGGINFACTOR  HELDA-GYFIPPENGGINFANGGINFANGGINFANGGINFACTOR  HELDA-GYFIPPENGGINFANGGINFANGGINFANGGINFANGGINFACTOR  HELDA-GYFIPPENGGINFANGGINF				
HELD LILPFILDA-GYFIPLAGFENDGTILFAVOTUNGAFFENGGINTACLOG  HE LILPFILDA-GYFIPLAGFENGGINFAVOTUNGATGGINAFFENGGINTACLOGIS  ANNISA LILPFIVLDA-GYFIPPENGGINFAVOTUNGATGGINAFFENGGINTACLOGIS  HELDA-GYFIPPENGGINFANGGINFAVOTUNGATGGINFACTOR  HELDA-GYFIPPENGGINFANGGINFANGGINFACTOR  HELDA-GYFIPPENGGINFANGGINFANGGINFANGGINFACTOR  HELDA-GYFIPPENGGINFANGGINFANGGINFANGGINFANGGINFACTOR  HELDA-GYFIPPENGGINFANGGINF		MA MS		
NHE LCLLPFILDA-GYTLPIRPTENWOTILVFAVICTAMAFFMGGLVALCOIES 184 NHES LEGAM LILPFYUDA-GYPHENFERFENGITYWAVOGUNANTICIOSAN 186 NHES PULPPYUDA-GYPHENFERFENGITYWAVOGUNANTICIOSAN 186 NHES PULPPIVOA-GYPHENALFFENGISILVAVOGUNANTICIOSAN 186 NHES PULPPIVOA-GYPHENALFFENGISILVAVOGUNANTICIOSAN 186 NHES PULPPIVOA-GYPHENALFFENGISILVAVOGUNANTICIOSAN 186 NHES WOLGOULIACLIFGITAGOPUN/LAVFEHHNELMILVFGESLIADATVU 29 NHEE WOLGOULIACLIFGITAGOPUN/LAVFEHHNELMILVFGESLIADATVU 29 NHEE WOLGOULIACLIFGITAGOPUN/LAVFEHHNELMILVFGESLIADATVU 29 NHEE WOLGOULIACLIFGITAGOPUN/LAVFEHNELMILVFGESLIADATVU 20 NHEE WOLGOULIACUT 20 NHEE WOLGOULIA	NHE1		216	
HRE2  LULLPYULG-GYPHTPEPPENLGTIFWIAVUTLNNSIGIOUSIGICOITA 196  HRE3  HRE3  HRE4  LULLPYULG-GYPHTPEPPENLGTIFWIAGUTHANTOIGLIFUTGAN  HRE5  LULLPYULGSGOTFENNALFENTBOTANTOIGSENTAGGALIAUTGATE  LULLPYULGSGOTFENNALFENTBOTANTOITANTOIGLIFUTGAN  HRE5  EGINNIGLIONLIFESIISANDOVAVLAVPEHHNELHILUTGESLIAUTATV  HRE6  HRE9  HRE9  HRE9  LULLPYULGSSUTSANDOVAVLAVPEHHNELHILUTGESLIAUTATV  HRE9  HRE9  VOLSGOTLIACLIFESIISANDOVAVLAVPEHHNELHILUTGESLIAUTATV  HRE9  HRE1  HRE1  LUTHIPEPENLALIAUTAVAFEHHNELHILUTGESLIAUTAVT  HRE2  FULGOTILLAULIFESIISANDOVAVLAVPEHHNELHILUTGESLIAUTAVT  HRE4  HRE6  HRE7  LUTHIPEPENLALIAUTAVAFEHHNELHILUTGESLIAUTAVT  HRE7  LUTHIPEPENLALIAUTAVAFEHHNELHILUTGESLIAUTAVT  HRE7  HRE7  LUTHIPEPENLALIAUTAVAFEHHNELHILUTGESLIAUTAVT  HRE7  LUTHIPEPENLALIAUTAVAFEHHNELHILUTGESLIAUTAVT  HRE7  LUTHIPEPENLALIAUTAVAFEHHNELHILUTGESLIAUTAVT  HRE7  HRE7  LUTHIPEPENLALIAUTAVAFEHHNELHILUTGESLIAUTAVAT  HRE7  HRE7  HRE7  HRE7  HRE7  HRE7  LUTHILIATTOMISUTAVAFEHHNELHILUTGESLIAUTAVAT  HRE7  H				
LILLIPFULES-GYPHTEPFPFENISGILWANGILALINAFGIGLEFFCOLTA HEBS FLIPPYLDA-GYPHENETFFENISGILWANGICHANTGISLUFFCIST ELGOAN LILLIPFITOSSOTHERNALFENIDOTUPESPOTTHERTAGGSLLIMACTOL  ### HEBS ### H				
FYLLPFIVLDA-GYPENRALFENIGSILLYAVGTVANAATTGIGLIGGT 169  LILPFITGSSEYENNAALFENIGSULVAVGTVANAATTGIGGLIGGT 169  LILPFITGSSEYENNAALFENIGSULVAVGTVATTAGGGLIGGT 169  WHEL MISSE GUNIGLLDLIFGSISAMDVAVLAVFEEHHELHILVTGSSLIADAVTV 239  WHEL COLONIGLUDLIFGSISAMDVAVLAVFEEHHELHILVTGSSLIADAVTV 239  WHEL WILSE GUNIGLLDLIFGSISAMDVAVLAVFEEHHELHILVTGSSLIADAVTV 239  WHEL WILSE GUNIGLLONLIFGSISAMDVAVLAVFEEHHELHILVTGSSLIADAVTV 239  WHEL WILSE GUNIGLUDLIFGSISAMDVAVLAVFEEHHELHILVTGSSLIADAVTV 230  WHEL WILSE GUNIGLUDLIFGSISAMDVAVLAVFEEHHELHILVTGSSLIADAVTV 240  ELEGAN FYMS-FTTFELLYFSALIANDVAVLAVFEEHHELFITYTGSSLIADAVTV 240  ELEGAN FYMS-FTTFELLYFSALIANDVAVLAVFEEHHELFITYTGSSLIADAVTV 240  WHEL WILSE GUNIGLUDLIFGSISAMDVAVLAVFEEHHELFITYTGSSLIADAVTV 240  WHEL WILSE GUNIGLUDLIFGSISAMDVAVLAVFEEHHELFITYTGSSLIADAVTV 240  WHEL WILSE GUNIGLUD FYMS-FTTFELLYFSALIADAVTV 240  WHEL WILSE GUNIGLUD FYMS-FTTFELLYFSALIADAVTV 240  WHEL WILSE GUNIGLUD FYMS-FTTFELLYFSALIADAVTV 240  WILSE GUNIGLUD FYMS-FTTFELLYFTTFT 240  WILSE GUNIG FYMS-FTTFFTTFT 240  WILSE GUNIG FYMS-FTTFFTTFT 240  WILSE GUNIG FYMS-FTTFTTFT 240  WILSE GUNIG FYMS-FTTFT 24				
LILDPHIPSSOYPHNRALPENDSVLVESVEGTINNFALGGSLLMAGTDL  MS.  MS.  MS.  MS.  MS.  MS.  MS.  MS	NHE3	FYLLPPIVLDA-GYFMPNRLFFSNLGSILLYAVVGTVWNAATTGLSLYGVFLSGI		
HEE EQUNITICALIDATES STANDWAY AND PERHAMELHAT LOPES LABORYTY 271 HHEE VOLGOVILLACLINGSITS AND PARALAY PERHAMELHAT LOPES LABORYTY 271 HHEE VOLGOVILLACLINGSITS AND PARALAY PERHAMELHAT LABORS YELD STANDWAY AND PERHAMEN STANDWAY STANDWAY SANDWAY SAND	ELEGAN			
HNEL EQINNICLIONLEGSITANOPVANIAFFERHINELLHILVTGESLINDAYTY HNE GISOVULLACILEGSITANOPVANIAFFERHINELHILVTGESLINDAYTY HNEL FELSOVILLACILEGSITANOPVANIAFFERHINELHILVTGESLINDAYTY HNEL FELSOVILLACILEGSITANOPVANIAFFERHINELHILVTGESLINDAYTY HNEL FELSON FYMS-FTTELLYSILASANOPVANIAFFERHYNELHILVTGESLINDAYTY HNEL FELSON FYMS-FTTELLYSILASANOPVANIAFFERHYNELFILVTGESLINDAYTY HNEL VLYNLFSERSHYONVCIVOLVLGTLSFFVVALGANIAFTSKYPT HNEL VLYNLFFERSKYONVCIVOLVLGTLSFFVVALGANIVGTIVAFFANNOPY HNEL VLYNLFRSEGNATHIETIDVARGIANFFVVIGGAULVGALVGFLAAFTSKYPT HNEL VLYNLFRSEGNATHIETIDVARGIANFFVVIGGAULVGALVGFLAAFTSKYPT HNEL VLYNLFRSEGNATHIETIDVARGIANFFVVIGGAULVGALVGFLAAFTSKYPT HNEL VLYNLFRSEGNATHIETIDVARGIANFFVVIGGAULVGALVGFLAAFTSKYPT HNEL VLYNLGAGEGNATURGANVCHOVENGVERFVVSLAGANVGALTGFLAAFTSKYPT HNEL VLYNLGAGEGNATURGANVGARGANVGALVGARVGARTHATAASLITKYT HNEL VLYNLGAGEGNATURGARTHAGANVGARVGARVGATTAASLITKYT HNEL WARNOFSTALGSENLSVLOYANGGLSFFVVALGGAAVGALTGFLAASLITKYT HNEL WARNOFSTALGSENLSVLOYANGGLSFFVVALGGAAVGARVGAVGANTSKYT HNEL WARNOFSTALGSENLSVLOYANGGLSFFVVALGGAAVGARVGAVGANTSKYT HNEL WARNOFSTALGSENLSVLOYANGGLSFFVVALGGAAVGARVGAVGANTSKYT HNEL WARNOFSTALGSENLSVLOYANGGLSFFVALGGAAVGARVGAVGANTSKYT HNEL WARNOFSTALGSENLSVLOYANGGLSFFVALGGAAVGARVGAVGANTSKYT HNEL WARNOFSTALGSENLSVLOYANGGLSFFVALGGAAVGARVGAVGANTSKYT HNEL WARNOFSTALGSENLSVLOYANGGLSGATAFTURGATAASLITKYT HNEL WARNOFSTALGSENLSVLOYANGGLSGATAFTURGATAASLITKYT HNEL WARNOFSTALGSENLSVLOYANGGLSGATAFTURGATAASLITKYT HNEL WARNOFSTALGSTALGSENLSSALATAGGAAVGARVGAVGANTSKYTHATAASLITKYT HNEL WARNOFSTALGSTALGSTALGSALATAGGAAVGARVGAVGANTSKYTHATAASLITKYT HNEL WARNOFSTALGSTALGSTALGSTALGAGAAVGARVGAVGANTSKYTHATAASLITKYT HNEL WARNOFSTALGSTALGSTALGSTALGAGAAVGARVGATAATGAATAGAAVGATATGAATAGAAVGATATGAATAGAAVGATATGAATAGAAVGATATGAATAGAAVGATATGAATAGAAT		. ***** . *** * * * * . * .		
HNEL EQUINITGLIONLIFGSITANOPVANIAFFEITHERLHITUTGESLIDANTY HNE GIGSUTLIACHLESITANOPVANIAFFEITHERLHITUTGESLIDANTY HNEL FGLSDTLIACHLESITANOPVANIAFFEITHERLHITUTGESLIDANTY HNEL FGLSDTLIACHLESITANOPVANIAFFEITHERLHITUTGESLIDANTY HNEL FGLSDTLIACHLESITANOPVANIAFFEITHERLHITUTGESLIDANTY HNEL FGLSDTLIACHLESITANOPVANIAFFEITHERLHITUTGESLIDANTY HNEL FERNAMYORVGIVOIVLOTLSFEVNALGANOPVENTURFITHERLHIDANTY HNEL VLYNLFFERMYORVGIVOIVLOTLSFFVNALGANOPVENTURFITHERLHIDANTY HNEL VLYNLFFSKVGTUTULDTLGTUSFFVNALGANOVUNGVIGHAAFTSKFF HNEL VLYNLFKSFGGMANFEITUTGANIAFFVGGAULVGAIVGFLAAFTSKFF HNEL VLYNLFKSFGGMANFEITUTGANIAFFVGGAULVGAIVGFLAAFTSKFF HNEL VLYNLFKSFGGMANGAINFVNALGANIAFFTKFT HNEL VLYNLFKSFGGMANGAINFVNALGANIAFFTKFT HNEL VLYNLFSHGGANVGAULVGAIVGFFVNALGANVGAITFALASLITKTT HNEL VLYNLFSHGGANVGAULVGAIVGFFVNALGGANVGAITFALASLITKTT HNEL WINGVESTURGSENSVLOVATGGLSFFVNALGGANVGAITFALASLITKTT HNEL HNINVIEDLFYPLNSVANVLSAELFHLAGIALAAGUVAGDPVENATISHKSHTT HNEL HNINVIEDLFYPLNSVANVLSAELFHAGAIAAGUVAGDPVENATISHKSHTT HNEL HNINVIEDLFYPLNSVANVLSAELFHAGAIAAGUVAGDPVENATISHKSHTT HNEL HNINVIEDLFYPLNSVANVLSAELFHAGAIAAGUVAGDPVENATISHKSHTT HNEL HNINVIEDLFYPLNSVANVLSAELFHAGAIAAGUVAGDPVENATISHKSHT HNEL HNINVIEDLFYPLNSVANVLSAELFHAGAIAAGU		M5a M5b		
NHE VGLSGUDLACLICSISTSYAPPANLAVFERINNEUVHILVPGSSLINDAVTY NHE2 FGLGDITLICALICSISTAYOPVANLAVFERINNEUVHILVPGSSLINDAVTY 251 ATTHRE4 FGLGDITLICALICSISTAYOPVANLAVFERINNEUPHTIPGEALINDAVTY 252 ATTHRE4 FGLGDITLICALICSISTAYOPVANLAVFERINNEUPHTIPGEALINDAVTY 253 ATTHRE4 FGLGDITLICALICSISTAYOPVANLAVFERINNEUPHTIPGEALINDAVTY 264 BLEGGAN PWG-FTFFEHICAGLANDAVALAVFERINNEUPHTIPGEALINDAVTY 255 BLEGGAN VLYHLFEERINUDWACUTDIVLGFLAFFRUNGEFLANGEVENVANGUAAFTSRFT 258 BLEGGAN VLYHLFEERINUDWACUTDIVLGFLAFFRUNGEFLANGEVENVANGUAAFTSRFT 259 BLEGGAN VLYHLFEERINUDWACUTDIVLGFLAFFRUNGEFLANGEVENVANGUAAFTSRFT 269 BLEGGAN VLYHLFEERINUDWACUTDIVLGFLAFFRUNGEFLANGEVENVANGUAAFTSRFT 260 BLEGGAN VLYHLFEERINUDWACUTDIVLGFLAFFRUNGEFLANGEVERINFET 260 BLEGGAN VLYHLFEERINUDWACUTDIVLGFLAFFRUNGEFLANGEVERINFET 260 BLEGGAN VLYHLGANGUSTULG-DKYNGDCVAGIVSFFVULGGANVGITFATAASLITKYT VLYQC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYQC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYQC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGITFATAASLITKYT VLYGC-SKRA-LIGSENLSVLDYATGGLSFFVALGGANVGANGGANVGANGGANGGANGGANGGANGGANGGAN	NHE1		271	
HREI MEGLEGIALGYLLFSSLIANDFVATLAVPERANVEQLYMPITGERLINDGTSV 224  BLECAN FYMS-PTTEILYFSALIANDFVATLAVERSWYNEQLYMPITGERLINDGTSV 224  BLECAN FYMS-PTTEILYFSALIANDFVATLAVERSWYNEQLYMPITGERLINDGTSV 224  BLECAN FYMS-PTTEILYFSALIANDFVATLAVERSWYNEQLYMPITGERLINDGTSV 224  BLECAN FYMS-PTTEILYFSALIANDFVATLAVERSWYNEGLYMPITGERLINDGTST 224  BHE VLYNLFEERSKVCHTVTLOVELGVICFISFFVALGGVIVGALTGFLAAFTSRFT 205  BHE VLYNLFSEGNATIFDITVAGALNFFVALGGVIVGALTGFLAAFTSRFT 205  BHE VLYNLFSEGNATIFDITVAGALNFFVALGGVIVGALTGFLAAFTSRFT 205  BHE VLYNLFSEGNATHIFDITVAGALNFFVALGGVIVGALTGFLAAFTSRFT 205  BHE VLYNLFSEGNATH	NHE		239	
MREI WINFEERANVENTUUDVILOYEDVINVELTINVESELLINDATV  153  MREI VLWILFEERANVENTUUDVALAVESEUNVELTINVESELLINDATV  154  MREI VLWILFEERANVENTUUDVILOYISTISTUVALAGUVVAVVALAAPTSEFT  155  MRE VLWILFEERANVENTUUDVILOYISTISTUVALAGUVVAVVAVALAAFTSEFT  156  MRE VLWILFEERANVENTUUDVILOYISTISTUVALAGUVVAVVAVALAAFTSEFT  157  MRE VLWINFEERANVENTUUDVILOYISTISTIVALAGUVVAAVVAAATSEFT  158  MRE VLWINFEERANVENTUUDVILOYISTISTIVALAGUVVAAVVAAATSEFT  159  MRE VLWINFEERANVENTUUDVAGINSTFYVALAGUVVAAVVAAATSEFT  150  MRE VLWILLAATUMATERE PETIOVPAGINNFTVVGGGVILGITLOFIAAFTSEFT  150  MRE VLWILLAATUMATERE PETIOVPAGINNFTVVGGGVILGITLOFIAAFTSEFT  150  MRE VLWINFESTVILGG-DEVITOVCKGIVSFFVALAGANGGITAATAASLITTKY  150  MRE VLWINFESTVILGG-DEVITOVCKGIVSFFVALAGANGGITAATAASLITTKY  150  MRE VLWINFESTVILGG-DEVITOVCKGIVSFFVALAGANGGITAATAASLITTKY  151  MRE SETTUUTBEFFVILSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  152  MRE SETTUUTBEFFVILSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  153  MRE SETTUUTBEFFVILSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  154  MRE SETTUUTBEFFVILSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  155  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  156  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  157  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  158  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  159  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  150  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  154  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  156  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  157  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVVBANISHKSHTT  157  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVBANISHKSHTT  157  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVBANISHKSHTT  157  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVBANISHKSHTT  159  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVBANISHKSHTT  150  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAGONVAGPVBANISHKSHTT  151  MRE SETTUUTBEFFVINSTMANISSERFELGGINALAAG	NHE2			
FYMS-PTTEILYFSALLSANDFVAVIAVEELHVWEELFINVGCALENDGTV  ***********************************				
NNE1 VLYNLFEEFANVDHVGIVDIVGITASFTWALGGUVEGVVTAGVTAAFTSRFT NNE2 VLYNLFEESKVCTVTYLOVEGVUTGVTAGATSRFT NNE2 VLYNLFEESKVCTVTYLOVEGVAGATSRFT NNE2 VLYNLFEESKVCTVTYLOVEGVAGIANFTVAGGUVLGGIVAGATSRFT 103 NNE2 VLYNLFEESKVCTVTYLOVEGVAGIANFTVAGGUVLGGIVAGATSRFT 104 NNE2 VLYNLFEESKVCTVTYLOVEGVAGIANFTVAGGUVLGGIVAGATSRFT 105 NNE2 VLYNLFEESKVCTVTYLOVEGVAGIANFTVAGGUVLGGIVAGATSAFTSTFT 106 NNE2 VLYNLFEESKVCTVTYLOVEGVAGIANFTVAGGUVAGATGATATTT 107 NNE2 VLYNLFEESKVCTVTYLOVEGVAGIANFTVAGGANGVIFAFAASLITKYT 108 NNE2 VLYNLFEESKVCTVTYLOVEGVAGIANFTVAGGANGVIFAFAASLITKYT 108 NNE2 SHTRVIEPLFYFIYSYMAYLSEENFHLSGIRALLAGGVVRRPYVEANISHKSFTT 108 NNE2 SHTRVIEPLFYFYSYMAYLSEENFHLSGIRALLAGGVVRRPYVEANISHKSFTT 108 NNE2 SHTRVIERLFYFAGYSVAGSHHWWWFFYITTYLLGVSRVLGGUG 109 NNE2 SKYFRANGSSVSETLIFIFLGYSTVAGSHHWWWFFYITTYLLGVSRVLGGUG 109 NNE2 SKYFRANGSSVSETLIFIFLGYSTVAGSHHWWWFFYITTYLLGVSRVLGGUG 109 NNE2 SKYFRANGSSVSETLIFIFLGYSTVAGSHHWWWFFYITTYLLGVSRVLGGUG 109 NNE2 SKYFRANGSSVSETLIFIFLGYSTVAGSHHWWWFFYITTYLLGVSRVLGGUG 109 NNE2 SKYFRANGSSVSETLIFIFLGSTVAGSHWWWFFYITTYLLGVSRVLGGUG 109 NNE2 SKYFRANGSSVSE				
NHEL VLYHLEEPAN.—VJOHYOTULAFISFTVVALGGVFVGVVGGVTAAFTSRT  WHE VLYHLEEPAN.—VJOHYOTULAFTSFTVVALGGVFVGVVGGVTAAFTSRT  WINTERSFORMST - TITLDYSTAINTFVVVALGGVFTGVTAAFTSRT  WINTERSFORMST - TITLDYSTAINTFVVALGGVTGVTGTTAAFTSRT  WINTERSFORMST - TITLDYSTAINTFVVALGGVTGTTGTTSAFTTRFT  WINTERSFORMST - TITLDYSTAINTFVVALGGVTGTTGTTSAFTTRFT  WINTERSFORMST - TITLDYSTAINTFVALGGVTGTTGTTSAFTTRFT  WINTERSFORMST - TITLDYSTAINTFVALGGVTGTTGTTSAFTTRFT  WINTERSFORMST - TITLDYSTAINTFVALGGAAVGTTGAAASLTTRYT  WINTEL AHTRVIEPLFVFLYSYMAVISSELFFLSGTMALTAGGVVRGPYVEANTSHKSHTT  WHE SHTRVIEPLFFVLYSYMAVISSELFFLSGTMALTAGGVVRGPYVEANTSHKSHTT  WHE SHTRVIEPLFVFLYSYMAVISSELFFLSGTMALTAGGVVRGPYVEANTSHKSHTT  WHE SHTRVIEPLFVFLYSYMAVISSELFFLSGTMALTAGGVVRGPYVEANTSHKSHTT  WHE SHTRVIEPLFVFLYSYMAVISSELFFLSGTMALTAGGVVRGPYVEANTSHKSHTT  WHE SHTRVIEPLFVFLYSYMAVISSELFFLSGTMALTAGGVVRGPYVEANTSHKSHTT  WHE SHTRVIEPLFVFLYSYMAVISSELFFLSGTMALTAGGVVRGPYVEANTSHKSHTT  WHE SHTRVIEPLFVFLYSTMATHAGENSISSITATAGGTMATNKYVEENWSGTSSTTT  JSG  WHEL KYFLKHMSSVSETLIFIFLGVSTVAGSHWHNTFVITTVLCIVSRVLGVLG  WHE IKYFLKHMSSVSETLIFIFLGVSTVAGSHWHNTFVITTVLCIVSRVLGVLG  WHE IKYFLKHMSSVSETLIFIFLGSTAND-PLUTWAHTAFVRLTLIFLFVGVFLAGTUV  WYTTSTALAGGSTTIFFFUTGTSAND-PLUTWAHTAFVRLTLIFFTGTSATUV  WYTTSTALAGGSTTIFFFUTGTSAND-PLUTWAHTAFVRLTLIFFTGTSATUV  WYTTSTALAGGSTTIFFFUTGTSAND-PLUTWAHTAFVRLTLIFFTGTSATUV  WYTTSTALAGGSTTIFFTGTSTSSGHHFDLYFLCATLFFFCLIVATATUV  WYTTSTALAGGSTTIFFTGTSTSSGHHFDLYFLCATLFFFCLIVATATUV  WYTTSTALAGGSTTIFFTGTSTSSGHHFDLYFLCATLFFFCLIVATAGTUV  WYTTSTALAGGSTTIFFTGTSTAGGSTGSTANDAFTGTATTTT  WHE IKTTLIFFTGTTFTCDTFTCDGTTGTTGTTGTTTTT  WHE IKTTLIFFTGTTFTCDGTTGTTGTTGTTGTTTTTT  WHE IKTTLIFFTGTTTFTCDGTTGTTGTTGTTGTTTTT  WHE IKTTLIFFTGTTTTTTTTTT  WHE IKTTLIFFTG	ELEGAN		153	
NHEL VLYHLEPEPANYDHVIJOUTUGFISFVVALGGVVGVYGVYAVAFSRFT 221 NHEZ VLYNLEPEPANVGTVYLVDVFGVGVGFVGVGGVULGTILGFIAFTRFT 221 NHEZ VLYNLEFEGGWKTIETIDVFGGTAHFFVGLGGVLGIFLGFIAFTRFT 225 NHEZ VLYNLIFEFAN-LESENLSVIDVATGGLFFVALGGAVGTFTATTT 228 NHEZ VLYNYGFFVLGG-KVTGVDCVKGTVSFVYSLGGTLGVGVFFAFTARFT 226 NHEZ VLYNYGFFVLGG-KVTGVDCVKGTVSFVYSLGGTLGVGVFFAFTARFT 226 NHEZ VLYNYGFFVLGG-KVTGVDCVKGTVSFVYSLGGTLGVGVFFAFTARFT 226 NHEZ VLYNYGFFVLGG-KVTGVDCVKGTVSFVYSLGGTLGVGVFFAFTARFT 226 NHEZ VLYNYGFFVLGG-KVTGVDCVKGTVSFVYSLGGTLGVGVFFAFTARASLTTKT 226 NHEZ AHTRVIEPLFVFLYSYMAYLSSEMFHLSGINALLAGGAVGHFPYVEANISHKSHTT 226 NHEZ HNTRVIEPLFVFLYSYMAYLSSEMFHLSGINALLAGGAVGHFPYVEANISHKSHTT 346 NHEZ HNTRVIEPLFVFLSSYMAYLSSEMFHLSGINALLAGGAVGHFPYVEANISHKSHTT 350 NHEZ HNTRVIEPLFVFLSSYMAYLSSEMFHLSGINALLAGGVVGRPYVEANISHKSHTT 350 NHEZ HNTRVIEPLFVFLSSYTARHHLSGINALTAGAMTHKKYVEENVGGKSTT 350 NHEZ HNTRVIEPLFVFLSSYTARHHLSGINALTAGAMTHKKYVEENVGGKSTT 350 NHEZ HNTRVIEPLFVFLSSYTAGSHHWM-TFVSTLTFLGAVTKGVTGAAANS 361 NHEZ HXFFLMMSSVSETLIFIFLGVSTVAGSHHWM-TFVSTLTFLGAVTGVGVG 341 NHEZ HXFFLMMSSVSETLIFIFLGVSTVAGSHHWM-TFVSTLTFLGAVGTVGVG 341 NHEZ HXFFLMMSSVSETLIFIFLGVSTVAGSHHWM-TFVSTLTFLGAVGTVGVG 341 NHEZ HXFFLMMSSVSETLIFIFLGVSTVAGSHHWM-TFVSTLTFLGAVGTVGVG 341 NHEZ HXFFLMMSSVSETLIFIFLGVSTVAGSHHWM-TFVSTLTFLGAVGTVGVG 341 NHEZ HXFFLMMSSVSETLIFIFLGVSTVAGSHHWM-TFVSTLTFLGAVGVGVG 341 NHEZ HXFFLMMSSVSETLIFIFLGVSTVAGSHAGATAGGLVGVGVGVG 341 NHEZ HXFFLMMSLAGGARGATIFFMAGTAGGARGATAFGLGAVGFT 341 NHEZ HXFFLMMSLAGGARGATIFFMAGTAGGARGATAGGAVGTVSLFFAAVFT 342 NHEZ HXFFLMGALGGARGATAGGAAAGGATAGGAAAGGATAGGAAGGAAGGAA		, , , , , ,		
NHE ULYNLEPEFSKUGTUVLLDYLGYUGFVUSLGGULUGALYGFLAFTSRFT 291 ATNREA ULYNLLAFTKHEREDIGAVDILAGCARFVIVOCGGVETAFTTST 295 NHEI ULYNLAFTKHEREDIGAVDILAGCARFVIVOCGGVETAFTTST 295 NHEI ULYNVOGSTUGG-GKVTGYGVUCKGUSFFVVALGGAAVGIIFALASLTTRYT 206  NHEI AHTRUIEPLFVELYSYMAYLSSENHFLSGINALLAGGVVRRPYVEANISHKSHTT 278 NHEI AHTRUIEPLFVELYSYMAYLSSENHFLSGINALLAGGVVRRPYVEANISHKSHTT 378 NHEI SHTRVIEPLFVELYSINJANTAGSINALLAGGVVRRPYVEANISHKSTT 358 ATNHEA QNISAITEPLTVMFSYLSSILAATAGAMTHKSGVARPYVEANISHKSTT 358 ATNHEA QNISAITEPLTVMFSYLSYLAATTLYLSGILAATAGAMTHKKYVEENVSGXSTT 350 NHEI KRYVILEFGVFLYSYLSYLAATTLYLSGILAATAGAMTHKKYVEENVSGXSTT 350 NHEI KRYVILEFGVFLYSILSILATAGATTHKKYVEENVSGXSTT 350 NHEI KRYFIKHMSSVSETLIFIGUSTVAGSHHNNW-TFVISTLIFGLIAVUGVLG NHEE KYFIKHMSSVSETLIFIGUSTVAGSHHNNW-TFVISTLIFGLIAVUGVLG NHEE KYFIKHMSSVSETLIFIFGVSTVAGSHHNNW-TFVISTLIFGLIAVUGVLG NHEE KYFHMLASSVSETLIFIFGVSTVAGSHHNNW-TFVISTLIFGLIAVUGVLG NHEE KYFHMLASSVSETLIFIFGVSTVAGSHHNNW-TFVISTLIFGLIAVUGVLG NHEE KYFHMLASSVSETLIFIFGVSTVAGSHHNNW-TFVISTLIFGLIAVUGVLG NHEE KYFHMLASSVSETLIFIFGNSTVGKNHENNM-FFVISTLIFGLIAVUGVLG NHEE KYFHMLASSVSETLIFIFGNSTVGKNHENNM-FFVISTLIFGLIAVUGVLG NHEE KYFHMLASSVSETLIFIFGNSTVGKNHENNM-FFVISTLIFGLIAVUGVLG NHEE KYFHMLASSVSETLIFIFGNSTVGKNHENNM-FFVISTLIFGLIAVUGVLG NHEE KYFHMLASSVSETLIFIFGNSTVGKNHENNM-FFVISTLIFGLIAVUGVLG NHEE LTPINKFRIVKLIPKDOPIIAYGGLAGATAFSLGYLLINGHPPMCDLEIDAITT NHEA ATNREA KYFTYMOHLASGATIFFHLOLSTISSGH-HFDLYFCATLFFCLIVARIGTVV 314  NHEL LTWINKFRIVLIPKDOPIIAYGGLAGAATAFSLGYLLINGH-PMCDLEIDAITT NHE LTPINKFRIVKLIPKDOPIIAYGGLAGAATAFSLGYLLINGH-PMCDLEIDAITT NHE LTPINKFRIVKLIPKDOPIIAYGGLAGAATAFSLGYLLINGH-PMCDLEIDAITT NHE LTPINKFRIVKLIPKDOPIIAYGGLAGAATAFSLGYLLINGH-PMCDLEIDAITT NHE LTPINKFRIVKLIPKDOPIIAYGGLAGAATAFSLGYLLINGH-PMCDLEIDAITT NHE VIPPTYFOGGTTRPLVDLLAVKKKESKFSINEEHTFTDFLLATATATA 368  NHEL WIPPTYFOGGTTRPLVDLLAVKKKCKESKFSINEEHTFTDFLUTATATATA 369  NHEL WIPPTYFOGGTTRPLVDLLAVKKKCKESKFSINEEHTFTDFLUTATATATA 369  NHEL GHHHWAGLARFNKYVYKKULAGERSEFEFEFT NHE HANDE HER GHHHWAGLAGATSPNAVYKVULAGARSFSINEHTFTDFLUTARAGATAGATAGATAGATAGATAGATAGATAGATAGATA	•			
NHEZ VLYNILIAFROYNKY TETIDVFAGIANFFYVOLGGVIGIFLEFIAAFTRFT 303 ANNEAS VLYNILIAFROHKFEDIEAND LAGCARFYLYCGGGVFGIFFEFIAFTRFT 295 NHEZ VLYNYUGGFTIGG-DKYNGVDCVKGIVSFFYVALGGAVGUFFALLSLYRRT 278 LEEGAN VLYNC-SKFA-LIGSENLSULDYATGGLSFFVVALGGAVGUFFALLSLYRRT 278 NHEZ VLYNCG-SKFA-LIGSENLSULDYATGGLSFFVVALGGAVGUFFALLSLYRRT 278 NHEZ VLYNCG-SKFA-LIGSENLSULDYATGGLSFFVVALGGAVGUFFALASLITKYT 206  NHEZ SHTRVIEPLFVFLYSYMAYLSSENFHLSGINALIAGGVVRRPYVEANISHKSHTT 378 NHEE SHTRVIEPLFVFLYSYMAYLSSENFHLSGINALIAGGVVRRPYVEANISHKSHTT 378 NHEE HNIRVIEPLFVFLYSYMAYLSSENFHLSGINALIAGGVVRRPYVEANISHKSHTT 356 NHREI HNIRVIEPLFVLYSYMAYLSSENFHLSGINALIAGGVVRRPYVEANISHKSHTT 356 NHREI KNYRVHERGFVFHISILSYLTSGHALTAGAMTKNKYVEENVGGVSTT 358 NHEE KNURVIERGFVFHISILSYLTSGHALTAGAMTKNKYVEENVGCTSTT 350 NHEEL KYFLAMMSSVSETLIFIRAVSTSSILATTGGLGCGKYVKANISEGSAT 333 NHREI KYFLAMMSSVSETLIFIRAVSTSSILATTGGLGCGKYVKANISEGSAT 333 NHREI KYFLAMMSSVSETLIFIRAVSTSGHANNA-FFVITTVILLIVSVLUGVIG 411 NHREI KYFLAMMSSVSETLIFIRAVSTVAGPHANNA-FFVITTVILLIVSVLUGVIG 411 NHREI KYFHAMLSSVSETLIFIRAVSTVAGPHANNA-FFVITTVILLIVSVLUGVIG 411 NHREI KYFHAMLSSVSETLIFIRAVSTVAGHRANNA-FFVITTVILLIVSVLUGVIG 411 NHREI KYFHAMLSSVSETLIFIRAVSTVAGNENNA-AFVCETLAFGLWSALGVFV 411 NHREI KYFHAMLSSVSETLIFIRAVSTVGANISHNA-FFVITTVILLIVSVLUGVIG 411 NHREI LTWFINKFRIVKLIKKNOGTURAVGGANAFFVITTALIVSVFAATGVAL 387 NHREI LTWFINKFRIVKLIKKNOGTURAGGLAGALAFSLUGVLISNSH-QRRHLEITAAIV 466 NHREI LTWFINKFRIVKLIKKNOGTURAGGLAGALAFSLUGVLISNSH-QRRHLEITAAIV 466 NHREI LTWFINKFRIVKLIKKNOGTURAGGLAGALAFSLUGVLISNSH-QRRHLEITAAIV 466 NHREI VIFFTVFQQMTITPLVURLUVKKKKSENFSNEEHTETLDHLLTAVGGUCCHY 508 NHREI VIFTVFQQMTITPLVURLUVKKKKSENFSNEEHTETLDHLLTAVGGUCCHY 508 NHREI VIFTVFQQMTITPLVURLUVKKKKESKPSINEEHTETLDHLLTAVGGUCCHY 508 NHREI GHHHKDRLNFRIKKVYKKCLIAGEBEREFUR KELKHARDHINSATEDVGGGGGGALAYGUVVSTPAS-ITRKPMTITATIA 588 NHREI GHHHKDRLNFRIKKVYKKCLIAGEBEREFUR KELKHARDHINSATEDVGGGGGGALAYGUVVSTPAS-ITRKPMTITATIA 588 NHREI GHHHKDRLNFRIKKVYKKCLIAGEBEREFUR KELKHARDHINSATEDVGGGGGGGALAYGUVVSTPAS-ITRKPMTITATIA 589 NHREI GHHHKDRLNFRIKKVYKKCLIAGEBEREFUR KELKHARDHINSATEDVGGGGGGGALAYGUVVST				
ATNRE4  VLYNIVGSVTLG-DAVTOUCKGUSFFYVSLGGTLGVUVFFFLISLUTET  NEE  BLEGAN  VLYQC-SKFA-LIGSENLSVLDYATGGLSFFVVALGGAAVGUTFALIAASLITKYT  NEE  AHRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGUVMFPYVEANISHKSHTT  NHE SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIASGUVWRFYVEANISHKSHTT  NHE SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIAGGVVWRFYVEANISHKSHTT  NHE SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIAGGVVWRFYVEANISHKSHTT  NHE SHTRVIEPLFVFLYSYLAAETLYLSGILAITACAVTHKKYVEENVGASTYT  NHEB (NISALEPLIVFHFSVLSYLAAETLYLSGILAITACAVTHKKYVEENVGASTYT  NHEB (NISALEPLIVFHFSVLSYLAAETLYLSGILAITACAVTHKKYVEENVGASTYT  NHEB (NISALEPLIVFHFSVLSYLAAETLYLSGILAITACAVTHKKYVEENVGASTYT  NHEB (NISALEPLIVFHFSVLSYLAAETLYLSGILAITACAVTHKKYVEENVGASTYT  NHEB (NISALEPLIVFHFSVLSYLAAETLYLSGILAITACAVTHKKYVEENVGASTYT  NHEB (NISALEPLIVFHFSUSYLAAETLYLGGILAGTACATHKKYVEENVGASTYT  NHEB (NISALEPLIVFHFSUSYLSHAETLATCGGLAGATKKYVEENVGASTYT  NHEB (NISALEPLIVFHFSUSYLSHAETLATCGGLAGATKKYVEENVGATATS  NHEI (KYFLKWMSSVSETLIFFIGUSTVAGSHHMNW—TFVISTLLFCLIARNLGVLG  NHEI (KYFLKWMSSVSETLIFFIGUSTVAGSHHMNW—TFVISTLLFCLIARNLGVLG  NHEI (KYFMMGLSSVSETLIFFIGUSTVAGSHHMNW—TFVISTLLFCLIARNLGVLG  NHEI (KYFMMGLSSVSETLIFFIGUSTVAGSHHMNW—TFVISTLLFCLIARNLGVLG  NHEI (KYFMMGLSSVSETLIFFIGUSTVAGSHHMNW—TFVISTLLCLUSKYLGVLG  NHEI (KYFMMGLSSVSETLIFFIGUSTVAGSHHMNW—TFVISTLLCLUSKYLGVLG  NHEI (KYFMMGLSSVETLIFFIGUSTVAGSHHMNW—TFVISTLLCLUSKYLGVLG  NHEI (KYFMMGLSSVETLIFFIGUSTVAGSHHMNW—TFVISTLLCLUSKYLGVLG  NHEI (KYFMMGLSSVETLIFFIGUSTVAGSHHMNW—TFVISTLLCLUSKYLGVLG  NHEI (KYFMMGLSSVETLIFFIGUSTVAGSLAGALAFSLGVLLLKHYSVFTALV  NHEI (LTWINNFRIVKLTKMDFIVAYGGLAGALAFSLGVLLLKHYSVFTALV  NHEI (LTWINNFRIVKLTKMDFIVAYGGLAGALAFSLGVLLLKHYSVFTALV  NHEI (LTWINNFRIPTLYFKDGFILAYGGLAGALAFSLGVLLLKHARTUTATIL  NHE (LTWINNFRIPTLYFKDGFILAYGGLAGALAFSLGVLLLKHARTUTATIL  NHE (LTWINNFRIPTLYFKDGFILAYGGLAGALAFSLGVLLLKHARTUTATIL  NHE (LTWINNFRIPTLFWOGHTHAGALAFSLGVLLKHARTUTATILAGALAFALTUTATILAGALAGATAVTLTAATATA  NHE (MINHEN MANUTALLTAATATATATATATATATATATATATATATATATA	NHE			
HEEGAN  VLYNCYGSFVALGSENLSVLDYATGGLSFYVALGGAVGIIFALASLITKYT  206  NHEL  AHIRVIEDLFUFLYSYMAYLSAELFHLSGIMALIASGUVMERPYVEANISHKSHTT  KIE  BETRVIEDLFUFLYSYMAYLSEMFHLSGIMALIASGUVMERPYVEANISHKSHTT  378  KIE  BETRVIEDLFUFLYSYMAYLSEMFHLSGIMALIASGUVMERPYVEANISHKSHTT  378  KIE  BETRVIEDLFUFLYSYMAYLSEMFHLSGIMALIASGUVMERPYVEANISHKSHTT  378  KIE  BETRVIEDLFUFLYSYMAYLSEMFHLSGIMALTACAUTHKKYVEENVSGKSYTT  378  KIE  BETRVIEDLFUFLSYMAYLSEMFHLSGIMALTACAUTHKYVEENVSGKSYTT  378  KIE  BELEGAN  VORISATEPLLYHFSYLSYMAYLSENLTSLSGILATTCGGICOGKVVEANISHSSGATT  383  SHRIE  KIEVERHYFFYLSYMAYLTARWYSLSSILATTCGGICOGKVVEANISHSSGATT  383  SHRIE  KIEVERHYFFYLSYMAYLTARWYSLSSILATTCGGICOGKVVEANISHSSGATT  383  SHRIE  KIEVERHYFFYLSYMAYLTARWYSLSSILATTCGGICOGKVVEANISHSGSATT  383  SHRIE  KIEVERHYFFYLSYMAYLTARWYSLSSILATTCGGICOGKVVEANISHSGSATT  389  NHEL  IKYFLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVISTLLFCLLTARVLGVLG  KIEVERHYSTARLSSTLIFFIFLGVSTVAGSHWNN—TFVISTLLFCLLTARVLGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVISTLLFCLLTARVLGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVITVILLCLVSRVLGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVITVILLCLVSRVLGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVITVILLCLVSRVLGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVITVILLCLUSALGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVITVILLCLUSALGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVITVILLCLUSALGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVITVILLCLUSALGVLG  431  SHRIE  KYPLKMMSSVSETLIFFIFLGVSTVAGSHWNN—TFVITVILLCLUSAGURG  534  SHRIE  KYPLKMMSSVSTLIFFIFLGVSTVAGSHWNN—TFVITVILLCLUSAGURG  534  SHRIE  KYPLKMMSSVSTLIFFIFLGVSTVAGSHWNN—TFVITVILLCLUSAGURG  536  SHRIE  KYPLKMSSVSTLIFFIFLG  537  SHRIE  KYPLKMSSVSTLIFFIFLG  538  SHRIE  KYPLKMSSVSTLIFFIFLG  538  SHRIE  KY				
NHEI AHIRVIEPLFVFLYSYMAYLSENFHLSGINALIASGVVRFPYVEANISHKSHTT NHEE SHTRVIEPLFVFLYSYMAYLSENFHLSGINALIASGVVRFPYVEANISHKSHTT NHEE SHTRVIEPLFVFLYSYMAYLSENFHLSGINALIASGVVRFPYVEANISHKSHTT 378 NHEE HNIBVIEPLFVFLYSYMAYLSENFHLSGINALIASGVVRFPYVEANISHKSHTT 378 NHEE HNIBVIEPLFVFLYSYMAYLSENFHLSGINALIASGVVRFPYVEANISHKSHTT 378 NHEE HNIBVIEPLFVFLYSYMAYLSENFHLSGINALIASGVVRFPYVEANISHKSYTT 378 NHEE HNIBVIEPLFVFLYSYMAYLSENFHLSGINALIASGVVRFPYVEANISHKSYTT 378 NHEE KNURAUEPGFVFLISTINGTHESHLSISSILATHROGICCQRYVRANISEGSART 373 NHEE KNURAUEPGFVFLISTINGTHESHLSISSILATHROGICCQRYVRANISEGSART 373 NHEE IKYFLKHMSSVSETLIFFFLGVSTVASSHWNW—TFVITSTLLFCLIARVLGVLG 379 NHEE IKYFLKHMSSVSETLIFFFLGVSTVASSHWNW—TFVITSTLLFCLIARVLGVLG 379 NHEE IKYFLKHMSSVSETLIFFFLGVSTVASSHWNW—TFVITSTLLFCLIARVLGVLG 379 NHEE IKYFLKHMSSVSETLIFFFLGVSTVASSHWNW—TFVITSTLLFCLIARVLGVLG 370 NHEE IKYFLKHMSSVSETLIFFFLGVSTVASSHWNW—TFVITSTLLFCLIARVLGVLG 370 NHEE IKYFLKHMSSVSETLIFFFLGVSTVASSHWNW—TFVITSTLLFCLIARVLGVLG 370 NHEE IKYFLKHMSSVSETLIFFFLGVSTVASSHWNW—TFVITSTLLFCLIARVLGVLG 370 NHEE IVYSTMCHLSSVSTLIFFFLGVSTVASSHWNW—TFVITSTLLFCLIARVLGVLG 370 NHEE ILFWINKLASGASTTIFFFLGISAVD—PLINTWNTAFVETLTLFYSVFRAIGVVL 387 NHEE ILFWINKFTIVKLTPEKDOFTLANGGLEGALAFSLGVLLDKKHFPMCDLFLTALTT 387 NHEE ILFUNKFFTIVTFTKDOFTLANGGLEGALAFSLGVLLDKKHFPMCDLFLTALTT 388 NHEE ILFUNKFFTIVTFTKDOFTLANGGLEGALAFSLGVLLDKKHFPMCDLFLTALTT 389 NHEE ILFUNKFFTIVTFTKDOFTLANGGLEGALAFSLGVLLDKKHFPMCDLFLTALTT 389 NHEE ILFUNKFFTIVTFTKDOFTLANGGLEGALAFSLGVLLDKKHFPMCDLFLTALTT 380 NHEE INTEL 380 NHEE 380 NHEE INTEL 380 NHEE 380 N				
NHEI AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIAGGVUMRPYVEANISHKSHTT NHE SHTKVIEPLFVFLYSYMAYLSEMFHLSGIMALIAGGVUMRPYVEANISHKSHTT NHE SHTKVIEPLFVFLYSYMAYLSEMFHLSGIMALIAGGVUMRPYVEANISHKSHTT ATNHEA QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTHKKVYEENVSQKSYTT ATNHEA QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTHKKVYEENVSQKSYTT 358 ATNHEA QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTHKKVYEENVSQKSYTT 359 NHEI KRYNICHT STATE				
NHEI AHTRVIEPLEVFLYSWAYLSAELFHLSGIMALIAGGVVRRPYVEANISKESTT 378 NHE SHRVIEPLEVFLYSWAYLSSEMFHLSGIMALIAGGVVRRPYVEANISKESTT 346 NHE2 HNIRVIEPLEVFLYSYSLSYTTAEMFHLSGIMALIAGGVRRPYVEANISKESTT 350 NHE3 KHRVIEPLEVFLYSSLSYTTAEMFHLSGIMALIAGGVRKYVEENVSGKSYTT 350 NHE3 KHRVIEPGFVFLISYMAYLTAEMTLSLSGILAITACOTKRKYVEENVSGKSYTT 350 NHE3 KHRVIEPGFVFLISYMAYLTAEMTSLSSILAITATGGICCQKVVKANISEQSATT 333 ELEGGAN VDVRILAPVIFFVLPYMAYLTAEMTSLSSILAITATGGICCQKVVKANISEQSATT 330 NHE1 IKVFLKMWSSVSETLIFFTGVSTVAGSHHWNN-TFVISTLLFCLIARVLGVLG 399 NHE1 IKVFLKMWSSVSETLIFFTGVSTVAGPHAWNN-TFVISTLLFCLIARVLGVLG 399 NHE1 IKVFKKMLSSVSETLIFFTGVSTVAGPHAWNN-TFVISTLLFCLIARVLGVLG 399 NHE2 IKVFKKMLSSVSETLIFFTGGVSTVGKNHEWNN-AFVCETLAFCLIKRALGVFV 411 ANNHE4 IKVFKKMLSSVSETLIFFTGGTSTAGPHAWNN-TFVISTLLFCLARVLGVLG 399 NHE2 WYTKMKLASSAETITFFTGLSATD-FLUTWINTAFFVALTLLFVSVFRAGVLGVLG 387 NHE3 WYTKMKLASSAETITFFTGLSATD-FLUTWINTAFFVALTLLFVSVFRAGVLGVLG 318 NHE2 WYTKMKLASSAETITFFTGLSATD-FLUTWINTAFFVALTLLFVSVFRAGVLU 317 NHE3 WYTKMKLASSAETITFFTGLSATD-FLUTWINTAFFVALTLLFVSVFRAGVLU 317 NHE2 LTFILNKFRLVKLTPKDOPTLAYGGLRGALAFSLGVLLSKHFPMCDLFLTAIT 496 NHE2 LTFILNKFRLVKLTPKDOPTLAYGGLRGALAFSLGVLLSKHFPMCDLFLTAIT 496 NHE2 LTFILNKFRLVKLTPKDOPTLAYGGLRGALAFSLGVLLSKHFPMCDLFLTAIT 450 NHE2 LTFILNKFRLVKLTPKDOPTLAYGGLRGALAFSLGVLLSKHFPMCDLFLTAIT 450 NHE2 LTFILNKFRLVKLTPKDOPTLAYGGLRGALAFSLGVLLSKHFPMCDLFLTAIT 450 NHE2 LTFILNKFRLVKLTPKDOPTLAYGGLRGALAFSLGVLLSKHFPMCDLFLTAIT 450 NHE2 UFFTVFVQGMTTRPLVSLLAVKKKGESFSLEHELTHFTGLDLLLTGUEGVCGHY 541 NHE3 WYFTVFTQGGTTTRLVVRTUKNGGFTGANFAFLVALLDGKKVKEKNHFVSTTII 442 NHE4 WYFTVFTFQGGTTTRLVVRTUKNGGFTGANFAFLVALLDGKKVKEKNHFVSTTII 442 NHE5 WYFTVFTQGGTTTRLVVRTUKNGGFTGANFAFLVALLDGKKVEKNHFTGEDVCGHW 5512 NHE5 WYFTVFTQGGTTTRLVVRTUKNGKGGRSFSLAFLLPLTLAFVRHMENGALAFLUKNGGFTGTTGANFAFLYNGKTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGTGTAGGTTGANFAFLYNGT				
NHEI AHTRVIEPLEVFLYSYMAYLSAELFHLSGIMALIAGGVVREPVZEANISKSHTT 378 NHE SHRVIEPLEVFLYSHAYLSSEMFHLSGIMALIAGGVVREPVZEANISKSYTT 346 NHE2 HNIRVIEPLEVFLYSHASYLTAEMFHLSGIMALIAGGVVREPVZEANISKSYTT 350 NHE3 KHRVIEPLEVFLYSHASYLTAEMFHLSGIMALIAGGVKTRKYVEENVSGKSYTT 350 NHE3 KHRVIEPGFVFLISYMAYLTAEMTYLSGIALATTACAVTRKKYVEENVSGKSYTT 350 NHE3 KHRVIEPGFVFLISYMAYLTAEMTYLSGIALATTACAVTRKKYVEENVSGKSYTT 350 NHE1 KHRVIEPGFVFLISYMAYLTAEMTYLSGIALATTACAVTRKKYVEENVSGKSYTT 350 NHE1 IKVFLKMWSSVSETLIFFTGVSTVAGHHWNN-TFVISTLLFCLIARVLGVIG 350 NHE1 IKVFLKMWSSVSETLIFFTGVSTVAGPHWNN-TFVISTLLFCLIARVLGVIG 350 NHE1 IKVFLKMWSSVSETLIFFTGVSTVAGPHWNN-TFVISTLLFCLIARVLGVIG 350 NHE2 IKVFKHMLSSVSETLIFFTGGVSTVGKHHENNN-AFVCFTLAFCLUKRALGVFV 411 ANNHE4 IKVFKKMLSSVSETLIFFTGGVSTVGKHHENNN-AFVCFTLAFCLUKRALGVFV 411 NHE1 IKVFKKMLSSVSETLIFFTGGVSTVGKHHENNN-AFVCFTLAFCLUKRALGVFV 314 NHE2 INVTNKHLASSAETLIFFTGISAVD-FLUTWINTAFVTLATLFVSVFRAGVUL 317 NHE3 WXTYKHLAGSSETLIFFTGISAVD-FLUTWINTAFVTLATLFVSVFRAGVUL 318 NHE3 WXTYKHMLAGSSETLIFFTGISAVD-FLUTWINTAFVTLATLFVSVFRAGVUL 317 NHE1 LTWFINKFRIVKLTPKDOFTIAVGGLGRATAFSLGVLLDKHFPMCDLFLTATIT 450 NHE2 LTFTINKFRIVKLTPKDOFTIAVGGLGRATAFSLGVLLDKHFPMCDLFLTATIT 451 NHE2 LTFTINKFRIVKLTPKDOFTIAVGGLGRATAFSLGVLLDKHFPMCDLFLTATIT 452 NHE2 LTFTINKFRIVKLTPKDOFTIAVGGLGRATAFSLGVLLDKHFPMCDLFLTATIT 453 NHE2 LTFTINKFRIVKLTPKDOFTIAVGGLGRATAFSLGVLLDKHFPMCDLFLTATIT 453 NHE2 LTFTINKFRIVKLTPKDOFTIAVGGLGRATAFSLGVLLSKHFPMCDLFLTATIT 454 NHE2 LTFTINKFRIVKLTPKDOFTIAVGGLGRATAFSLGVLLSKHFPMCDLFLTATIT 455 NHE2 WIFTVFTVFQGMTTRPLVSLLDAVKKKGESFSINEEIHTGFLDHLLTGGEDUCCHV 550 NHE2 WIFTVFTVFQGGTTTRLVVFRLAVKKKGEFKSINEEIHTGFLDHLLTGGEDUCCHV 551 NHE2 WIFTVFTVFQGGTTTRLVVFRLAVKKKGEFKSINEEIHTGFLDHLLTGGEDUCCHV 551 NHE3 WYFTVFTGGGTTTRLVVFRLAVKKKGEFKSINEEIHTGFLDHLLTGDEDUCCHV 551 NHE3 WYFTVFTGGGTTTRLVVFRLAVKKKGEFKSINEEIHTGBLKAGAFDVAGGGT 5512 NHE3 GHHWKEKLNFRKYVKKCLIAGENFKF-PP-LIAFYRMMEMQAIELVESGG 550 NHE2 GHHWKEKLNFRKYTVKRWILAGRNFFS-S-TVSLYKKLIDMLAGAIEVESGG 550 NHE2 GHHWKEKLNFRKFYTVKRWILAGRNFFS-S-TVSLYKRLIDMLAGAIEVESGG 550 NHE3 GHHWKELNFRKFPHFYLAKLIRBNGPSS-S-LVSLINGLEMGAIEVESGG 550 NHE3 GHHWKEL				
NHE				
AND	MUP?		270	
ANNHE4 QNISAIEPLIVPMFSYLSYLAAETLYLSGILAITACATTHKKYVEENVSGTSTTT NHE3 KYRVEVEEPFFYFIISYLYITSEHLSISSILAITACACCCQKVYKANISEGSATT S133 261  M8 MS 1 KYPLKUMSSVSETLIFIFGUSTVAGSHWNW-TFVISTLIFCLIARVLGVUG NHE1 IKYPLKWSSVSETLIFIFGUSTVAGSHWNW-TFVISTLIFCLIARVLGVUG NHE2 IKYPLKWSSVSETLIFIFGUSTVAGSHWNW-TFVISTLIFCLIARVLGVUG NHE2 IKYPLKWSSVSETLIFIFGUSTVGKNHEWNW-TFVISTLIFCLIARVLGVUG NHE2 IKYPRKMLSSVSETLIFIFWGVSTVGKNHEWNW-TFVISTLIFCLIARVLGVUG NHE3 VRYTMKMLASGAETLIFFRGUSTVGKNHEWNW-TFVISTLIFCLIARVLGVUV NHE3 VRYTMKMLASGAETLIFFRGUSTVGKNHEWNW-TAFVCFTLAFCLIWRALGVEV NHE3 VRYTMKMLASGAETLIFFRGUSTSGHHEWNW-TAFVCFTLAFCLIWRALGVEV NHE3 VRYTMKMLASGAETLIFFRGUSTSGHHEWNW-TAFVCFTLAFCLIWRALGVEV NHE4 LTWFINKFRIVKLITKKDQFILAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIT NHE6 LTFTINKFRIVKLITKKDQFILAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIT NHE6 LTFTINKFRIVKLITKKDQFILAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIT NHE6 LTFTINKFRIVKLITKKDQFILAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIT NHE6 LTFVINKFRIVKLITKKDQFILAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIT NHE6 LTFVINKFRIVKLITKKDQFILAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIT NHE7 LTVSNGFTFFFFSINGGLLIFYSGGARGSTSLAFLLFULTFFRKKLFVTATLV NHE8 QTWLLHRYBMVQLELIDQVVMSYGGLRGAYAFALVALLDGRKVWEKNLFVSTTII NHE8 QTVFLTFFGGTIIGFULTFFTGAGASTSLAFLFLTLTLFLTFRKFMFTTATA NHE1 NHE VIFFTTVFVGGMTIRPLVELLAVKKKQETKRSINEEIHTGFLDHLLTGVEGCGM NHE9 VYFFTTFFGGTIIGFLVRYLDVRKTNKKE-SINEEIHTGFLDHLLTGVEGCGGM NHE9 VYFFTTFFGGTIIGFLVRYLDVRKTNKKE-SINEEHHTGFLDHLLTGVEGCGGM NHE9 VYFFTTFFGGTIIGFLVRYLDVRKTNKKE-SINEEHHTGFLDHLLTGVEGCGGM NHE9 VYFFTTFGGTIIGFLVRYLDVRKTNKKE-SINEEHHTGFLDHLLTGVEGCGGM NHE9 CHYMWEKLNRFNKYVKKCLIAGERSKEPQ-LIAFYHKMEMKQAIEDUSGG NHE9 GHYBURDKKKYDKKYLLIRENQFKS-S-S-TVSLYKKLEKHAIEMAETM NHE1 GHHHWKDKLNRFNKKYVKKCLIAGERSKEPQ-LIAFYHKMEMKQAIEDUSGG NHU1EDKWKKRDDHTFLKLLKRGGNFFS-S-TVSLYKKLEKKHAIEMAETM NHE9 GHYBURDKKKRDDHTFLKLLIRENGFS-S-S-TVSLYKKLEKKHAIEMAETM NHE9 GHYBURDKKKRDDHTFLKLLIRENGFS-S-S-TVSLYKKLEKKHAIEMAETM NHE9 GHYBURDKKKRDDHTFLKLLIRENGFS-S-TVSLYKKLEKKHAIEMAETM NHE9 GHYBURDKKKRDDHTFLKLLIRENGFS-S-TVSLYKKLEKKHAIEMAETM NHE9 GHYBURDKKKRDDHTFLKLLKRGGRSKS-S-S-TVSLYKKLEKKHAIEMAETM NHE9 GHYBURDKKKRDDHTFLKL		AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT		
MES KHTWYLEPGFYFIISYLSYLTSEHLSLSSILAITCGLCQKYVKANISCGSATS ELEGAN YDVRILAPFYFIVLPWAYUTAEWVSLSSILAITCGLIMKQYIKGNTOAAANS 261  MES KYPIKMWSSVSETLIFIFIGVSTTVAGSHHWNW-TFVISTLIFCLIARVLGVLG NNEE IKYFIKMUSSVSETLIFIFIGVSTTVAGSHHWNW-TFVISTLIFCLIARVLGVLG NNEE IKYFIKMUSSVSETLIFIFIGVSTTVAGSHHWNW-TFVISTLIFCUIRALGVFV 411 ATNHE4 IKYFMKMLSSVSETLIFIFMGVSTTGKNHEWNW-AFVCFTLAFCLIWRALGVFV 411 ATNHE4 IKYFMKMLSSVSETLIFIFMGVSTTGKNHEWNW-AFVCFTLAFCLIWRALGVFV 411 ATNHE4 IKYFMKMLSSVSETLIFIFMGSTSTGKNHEWNW-AFVCFTLAFCLIWRALGVFV 411 ATNHE4 IKYFMKMLSSVSETLIFIFMGSTSTGKNHEWNW-AFVCFTLAFCQIWRALGVFV 411 ATNHE4 IKYFMKHLSGAGETIIFMFGLISAXD-PLLTWTWTAFFVTTLLIFVSVYFATGVVL 314  **********************************	NHE	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALTASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSYTT	346	
M8	NHE1 NHE NHE2	ahirvieplevelysymaylsaelehlsgimaliasgvvmrpyveanishkshtt strvieplevelysymaylssemfhlsgimaliacgvvmrpyveanishksytt hnirvieplevelysylsyitaemehlsgimaitacamtmkyveenvsqksytt	346 358	
M8	NHE NHE2 ATNHE4	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSYTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMNKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT	346 358 350	
NNE1 IXYFLKMMSSVSETLIFIFICUSTVAGSHANNWTFVISTLIFCLIARVLGVIG NNEE IXYFLKMMSSVSETLIFIFICUSTVAGPHANNWTFVITTVILCUSTRVLGVIG NNE2 IXYFKMLSSVSETLIFIFICUSTVAKHENNWAFVCFTLAFCLIWRALGVFV AITHE4 IKYFMKMLSSVSETLIFIFMCVSTVCKKHENNWAFVCFTLAFCCIWRALGVFV AITHE4 IXYFMKMLSSVSETLIFIFMCVSTVCKKHENNWAFVCFTLAFCCIWRALGVFV NNE3 VRYTKMLAGSAETIFMFIGISATD-FLIWTWNTAFVRITLIFVSVFRALGVVL NNE2 VKYFFKMLAGSSETVIFWFIGISTISSCHHFDLYFICATLFFVCLIYRAIGVVV NNEW LTFINKKFRIVKLTKKOQFFIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNE LTFINKKFRIVKLTKKOQFFIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFYNNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFVUNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFVUNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFVUNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFVUNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNES QTWLLNRYRMVQLELIDOVVMSVGGLRGAAVFALVALLDGNKVKEKNLFVSTTII 442 RLEGAN QCYILNRFRAKFENVDOFIMSVGGLRGAIAFSLGVLUSIFAS-ITRKPMFITATIA 368  ***********************************	NHE NHE2 ATNHE4 NHE3	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSYTT HIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMNKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT	346 358 350 333	
NNE1 IXYFLKMMSSVSETLIFIFICUSTVAGSHANNWTFVISTLIFCLIARVLGVIG NNEE IXYFLKMMSSVSETLIFIFICUSTVAGPHANNWTFVITTVILCUSTRVLGVIG NNE2 IXYFKMLSSVSETLIFIFICUSTVAKHENNWAFVCFTLAFCLIWRALGVFV AITHE4 IKYFMKMLSSVSETLIFIFMCVSTVCKKHENNWAFVCFTLAFCCIWRALGVFV AITHE4 IXYFMKMLSSVSETLIFIFMCVSTVCKKHENNWAFVCFTLAFCCIWRALGVFV NNE3 VRYTKMLAGSAETIFMFIGISATD-FLIWTWNTAFVRITLIFVSVFRALGVVL NNE2 VKYFFKMLAGSSETVIFWFIGISTISSCHHFDLYFICATLFFVCLIYRAIGVVV NNEW LTFINKKFRIVKLTKKOQFFIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNE LTFINKKFRIVKLTKKOQFFIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFYNNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFVUNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFVUNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFVUNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNEE LTFVUNWFRTTPLIFFKOQFIIAYGGLRGAIAFSLGYLLSNSH-OMRNLFITATIT NNES QTWLLNRYRMVQLELIDOVVMSVGGLRGAAVFALVALLDGNKVKEKNLFVSTTII 442 RLEGAN QCYILNRFRAKFENVDOFIMSVGGLRGAIAFSLGVLUSIFAS-ITRKPMFITATIA 368  ***********************************	NHE NHE2 ATNHE4 NHE3	AHIRVIEPLEVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSYTT HIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMKKYVEENVSQKSYTT QNISAIEPLLVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLITAEMVSLSSIIAIAICGMLMRQYIKGNVTQAAANS	346 358 350 333	
NHE	NHE NHE2 ATNHE4 NHE3	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFGGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAIAICGMLMKQYIKGNVTQAAANS	346 358 350 333	
NHE2 IKYFMKHLSVSETLIFIFMGVSTVGKHENNW-AFVCFTLAFCLIWRALGVFV 411 ARNHE4 IKYFMKHLSVSETLIFIFMGVSTVGKHENNW-AFVCFTLAFCQIWRALSVET 403 NHE3 VRYTMKHLSVSETLIFIFMGVSTVGKHENNW-AFVCFTLAFCQIWRALSVET 403 NHE3 VRYTMKHLSVSETLIFIFMGSTISSQH-HFDLYFICATLFFCLIYRAIGIVV 314  ** ** ** * * * * * * * * * * * * * *	NHE NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLEVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLEVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLEVFLYSYLSYITAEMFHLSGIMAITACAMTHMKYVEENVSQKSYTT QNISAIEPLLVFMFSYLSYLAAETLYLSGILAITACAVTHKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISGSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAIAICGMLMKQYIKGNVTQAAANS  * * * * * * * * * * * * * * * * * * *	346 358 350 333 261	
AUTHER	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1	AHIRVIEPLEVELVSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMKKYLENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFYLPYMAYLITAEMVSLSSILAITAICGMLMKQYIKGNVYQAAANS  M8  M9  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHAWNWTFVITTVILCLVSRVLGVIG	346 358 350 333 261	
NHE1	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE1	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMKKYVEENVSQKSYTT QNISAIEPLLVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEGSATT YDVRILAPVFIFYLPYMAYLTAEMVSLSSIIAIAICCMLMKQYIKGNVTQAAANS  *******  M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGSHAWNWTFVITTVILCLVSRVLGVIG IKYFKMLSSVSETLIFIFLGVSTVAGSHAWNWTFVITTVILCLVSRVLGVIG	346 358 350 333 261 431 399	
NHE1 LTWFINKFRIVKLTPKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT NHE2 LTFIINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLSNSH-QMRNLFLTAIIT AFANNHE4 LFYVSNGYFRIFPSIKQQLIFYSGVRGAGSFLAFLLPTLFPAKKFFTVATLV NHE3 QTWLLNRYEMVQLELIDQVVMSYGGLRGAIAFSLGYLLTLFPAKKFTVATLV NHE3 QTWLLNRYEMVQLELIDQVVMSYGGLRGAIAFSLGYLLFINFFRKKFFTAII AFA NHE4 QCYILNRFRAKKFEMVQDGFIMSYGGLRGAIAFSLGYLLVTLFPRKKKFTAITI AFA NHE1 VIFFTVFVQGMTIRPLVDLLAVKKKQETKRSINEEHHTQFLDHLLTGIEDICGHY NHE VIFFTVFVQGMTIRPLVELLAVKKKKSEKPSINEEHHTGFLDHLLTGUSGVCGHY NHE2 VIFFTVFILGITIRPLVEFLAVKKKKSEKPSINEEHHTGFLDHLLTGUSGVCGHY NHE2 VIFFTVFILGITIRPLVEFLAVKKKKESKPSINEEHHTGFLDHLLTGUSGVCGHY NHE3 VVFFTVFFQGITIGPLVRYLDVRKTNKKE-SINEELHTRLMDHLKAGIEDVCGOW NHE3 VVFFTVFFGGLTIKPLVQWLKVRNSHREFKLNEKLGRAFDHLLSAIEDISGQI ELEGAN WIYFTVFLGGITIRPLVFIKIKKKEERDFTMVESVYNKYLDYMMSGVEDIAGQK ******** ****** ***** ***** **** ***	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE1 NHE NHE2 ATNHE4	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCQKVYKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAIAICGMLMKQYIKGNVTQAAANS   MS  MS  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNWTFVITTVILCLVSRVLGVIG IKYFKKMLSSVSETLIFIFMCVSTVGKNIEWNWAFVCFTLAFCLIWRALGVFV IKYFMKMLSSVSETLIFIFMCVSTVGKNIEWNWAFVCFTLAFCLIWRALGVFV	346 358 350 333 261 431 399 411 403	
NHE1 LTWFINKFRIVKLTPKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT NHE LTFIINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLSNSH-QMRNLFLTAIIT NHE2 LTRVINWFRITPLIFTEDQFIIAYGGLRGAICFALVFLLPAAVPFRKKLFVTTAIU A66 ATNHE4 LFYUSNQFRTFPFSIKDQLIIFYSGVRGAGSFSLAFLLPLTLFPRKKLFVTATLU A58 NHE3 QTWLLNRYRMVQLELIDQVVMSYGGLRGAVAFALVALLDGHKVKEKNLFVSTTII A68 NHE3 QCYILNRFRAKKFEMVDQFIMSYGGLRGAVAFALVALLDGHKVKEKNLFVSTTII NHE VIFFTVFVQGMTIRPLVDLLAVKKKQETKRSINEEHHTQFLDHLLTGIEDICGHY NHE VIFFTVFVQGMTIRPLVELLAVKKKKESKPSINEEHHTEFLDHLLTGVEGVCGHY NHE2 VIFFTVFILGITIRPLVEFLDVKRSNKKQAVSEEHCRFFDHVKTGIEDVCGGW NHE3 VYFFTVFGGITIGPLVRYLDVKKTNKKE-SINEEHHTGFLDHLLAIEDUCGGW NHE3 VYFFTVFGGITIGPLVRYLDVKKTNKKE-SINEEHHTGHLDHLKAGIEDVCGGW NHE3 VYFFTVFQGITIRPLVBFLVKKTNKKE-SINEEHHTGHLDHLKAGIEDVCGGW NHE3 VYFFTVFQGITIRPLVFLDVKKTNKKE-SINEEHHTGHLDHLKAGIEDVCGGW NHE3 VYFFTVFQGITIRPLVFLOWKTNKKKE-SINEEHHTGHLDHLKAGIEDVCGGW NHE3 WIYFTVVLQGITIKPLVQWIKVKKRSERREPKINEKLHGRAFDHLISAIEDIGGG 497 ELEGAN WIYFTVYLQGITIRPLVFLINGKKYVKKEERDPTMVESVYNKYLDYMMSGVEDIAGGK 423 *** ** *** *** ** ** ** ** ** ** ** **	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE NHE NHE2 ATNHE4 NHE3	AHIRVIEPLEVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMKKYVEENVSQKSYTT QNISAIEPLLVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFYLPYMAYLITAEMVSLSSILAITAICGMLMKQYIKGNVYQAAANS  M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVITTUILCLVSRVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNW-TFVITTUILCLVSRVLGVLG IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCLIWRALGVFV IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCQIWRALSVFT URYTKKMLASGAETIIFMFUSISVGKNHEWNW-AFVCFTLAFCQIWRALSVFT VRYTKKMLASGAETIIFMFUSISVGKNHEWNW-AFVCFTLAFCQIWRALSVFT	346 358 350 333 261 431 399 411 403 387	
NHEE	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE NHE NHE2 ATNHE4 NHE3	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIAGGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMKKYVEENVSQKSYTT QNISAIEPLLVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFYLPYMAYLTAEMVSLSSIIAIAICCMLMKQYIKGNVTQAAANS  *********  M8  IKYFLKMWSSVSETLIFFFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFFFLGVSTVAGSHHWNWTFVITTVILCLVSRVLGVLG IKYFKKMLSSVSETLIFFFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFKKMLSSVSETLIFFFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFKKMLSSVSETLIFFFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWATAFVRLTLLFVSVFRAIGVVL VKYFFKMLAGSSETVIFMFLGISAVD-PLIWTWATAFVRLTLLFVSVFRAIGVVL	346 358 350 333 261 431 399 411 403 387	
NHE	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE NHE ATNHE4 NHE2 ATNHE4 NHE3	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIAGGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAMTMKKYVEENVSQKSYTT QNISAIEPLLVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFYLPYMAYLTAEMVSLSSIIAIAICCMLMKQYIKGNVTQAAANS  *********  M8  IKYFLKMWSSVSETLIFFFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFFFLGVSTVAGSHHWNWTFVITTVILCLVSRVLGVLG IKYFKKMLSSVSETLIFFFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFKKMLSSVSETLIFFFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFKKMLSSVSETLIFFFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWATAFVRLTLLFVSVFRAIGVVL VKYFFKMLAGSSETVIFMFLGISAVD-PLIWTWATAFVRLTLLFVSVFRAIGVVL	346 358 350 333 261 431 399 411 403 387	
NHE2 LTRVINWFRITPLTFKDQFILAYGGLRGATCFALVFLLPAAVFPRKKLFITAAIV 468 ATNHE44 LFYUSNQFRTFPFSIKDQLIIFYSGVRGAGSFSLAFLLPLTLFPRKKLFVTATLV 458 NHE3 QTWLLNRYRMVQLELIDQVVMEYGGLRGAVAFALVALLDGKKVEKKNLFVSTTII 442 ELEGAN QCYILNRFRAKKFEMYDQFIMSYGGLRGATAYGLVVSIPAS-ITRKPMFITATIA 368  *** *** *** *** **  M10  NHE1 VIFFTVFVQGMTIRPLVDLLAVKKKQETKRSINEEIHTQFLDHLLTGIEDICGHY 541 NHE VIFFTVFVQGMTIRPLVDLLAVKKKKESKPSINEEIHTEFLDHLLTGVBGVCGHY 508 NHE2 VIFFTVFTLGTITRFLVEFLDVKSINKXQAVSEEHHCRFFDHVKTGLDVCGHW 521 ATNHE4 VTYFTVFTGGITIGPLVRYLDVKRINKXQAVSEEHHCRFFDHVKTGLDVCGW 512 NHE3 VVFFTVIFQGITIRPLVVDLUKVKRSEHREPKLNEKLHGRAFDHILSAIEDISGQI 497 NHE3 VVFFTVIFQGITIRPLVNFLKIKKKESHPSINEEHHTRIMDHLKAGIEDVCGQW 512 NHE3 VVFFTVIFQGITIRPLVNFLKIKKKESHPSHTWSEVYNKYLDYMMSGVEDIAGQK 423  **** ** ** ** **  NHE1 GHHHWKDKLNRFNKKYVKKCLIAGERSKEPQ-LIAFYHKMEMKQAIENVESGG 593 NHE GHYHWKEKLNRFNKTYVKRWLIAGENFKEPS-LIAFYHKMEMKQAIENVESGG 560 NHE2 GHNFWDKKYFDHXILRILIRENQPKSSIVSLYKKLEHKQAIRMVESGG 560 NHE3 GHNYLRDKWANFDRRFLSKLIMRQSAGKSSDRILNVFHELNIKDAISYVTEGE 550 ATNHE4 SHYQVRDKFKKFDHXVIRKILIRENQPKSSIVSLYKKLEHKQAIRMVESGG 550 NHE3 GHNYLRDKWANFDRRFLSKLIMRQSAGKSRDRILNVFHELNIKDAISYVTEGE 550 ELEGAN GHYTFIENFERFNAKVIKPULMRHQKRESFDASSIVRAYEKITLEDAIKLAK  **  **  **  **  **  **  **  **  **	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE NHE2 ATNHE4 NHE3	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT RIRVIEPLFVFHSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFFIISYLSYLISEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAIAICGMLMKQYIKGNVTQAAANS  M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNWTFVITTUILCLVSRVLGVIG IKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV UKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VKYFKKMLAGSSETVIFMFLGISTUSGHHFDLYFICATLFFCLIVRAIGIVV  VKYFKKMLAGSSETVIFMFLGISTUSGHHFDLYFICATLFFCLIVRAIGIVV  ***  ***  ***  ***  ***  ***  ***	346 358 350 333 261 431 399 411 403 387	
ATMHE4  LFYUSNOFRTFPFSIKDQLIIFYSGVRGAGSFSLAFLLPLTLFPKKLFVTATLU  MHE3  QCYMLNRYRMVQLELLDQVUMVSVGGLRGAVAFALVALLDGKKVKEKLFVSTIII  442  ELEGAN  M10  NHE1  VIFFTVFVQGMTTRPLVDLLAVKKKQETKRSINEEHTTQFLDHLLTGJEDICGHY NHE VIFFTVFVQGMTTRPLVELLAVKKKESKPSINEEHTTGFLDHLLTGVEGVCGHV NHE2  VIFFTVFTGGITIGFLVRYLDVKKKKESKPSINEEHTTGFLDHLLTGVEGVCGHV 508  NHE2  VIFFTVFTGGITIGFLVRYLDVKKTNKKE-SINEEHTGFLDHKLTGJEDVCGGW 512  ANNHE4  VTYFTVFFGGITIGFLVRYLDVKKTNKKE-SINEEHTGFLDHKTGJEDVCGGW 512  NHE3  VVFFTVIFGGITIKPLVQWIKVKKRSEHTEFKLHGRAFDHLLSAIEDISGQI 497  ELEGAN  WIYFTVYLGGITTRPLVFFLKKKEERDPTMVESVYNKYLDYMMSGVEDLAGKK 23  *** ** *** ***  ***  ***  NHE1  GHHHWKDKLNRFNKKYVKKCLIAGERSKE-PQ-LIAFYHKMEMKQAIELVESGG SHHE GHYHWKEKLNFNKTVVKRWILAGENFKE-PE-LIAFYRKMELKQAIMMVESGQ 560  NHE2  GHNFWBKFKKFDKVLRKLILBROPKS-S-IVSLYKKLEHKALBMAETGM 572  ATMHE4  SHQVRDKFKKFDHXLRKLILBROPKS-S-IVSLYKKLEHKALBMAETGM 572  ATMHE4  SHQVRDKFKKFDHXLRKLILBROPKS-S-IVSLYKKLEHKALBMAETGM 572  ATMHE4  SHQVRDKFKKFDHXLRKLILBROPKS-S-IVSLYKKLEHKQAIEMAETGM 572  ATMHE4  SHQVRDKFKKFDHXLRKLILBROPKS-S-IVSLYKKLEHKQAIEMAETGM 572  ATMHE4  SHQVRDKFKKFDHXLRKLLIRROPKS-S-IVSLYKKLEHKQAIEMAETGM 572  ATMHE4  SHQVRDKFKKFDHXLRKLLIRROPKS-S-IVSLYKKLEHKQAIEMAETGM 572  ATMHE4  SHQVRDKFKKFDHXLRKLLIRROPKS-S-IVSLYKKLEHKQAIEMAETGM 572  NHE3  GHNYLFIENFERFRAKVIKFVUMRHQKRESFDASSIVRAYEKTILEDAIKLAK  **  **  **  **  **  **  **  **  **	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYLTAEMFHLSGIMAITACAMTMKKYLENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAUTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLFSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFYLPYMAYLTAEMVSLSSIIAIAICGMLMKQYIKGNVTQAAANS  M8  M9  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNW-TFVITTVLICLVSRVLGVLG IKYFKMMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTMKMLSSVSETLIFIFMGSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYFKMLASGAETIIFFMGUSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYFKMLASSETVIFMFLGLSTLSSQH-HFDLYFICATLFFCLIYRALGIVV  **	346 358 350 333 261 431 399 411 403 387 314	
NHE3	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE2 ATNHE4 NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLGAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITGGMLMKQYIKGNVTQAAANS  **********  M8  IKYFLKMWSSVSETLIFFFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVLG IKYFLKMWSSVSETLIFFFLGVSTVAGSHHWNWTFVITTULCLUSRVLGVLG IKYFLKMWSSVSETLIFFFLGVSTVAGPHAWNWTFVITTULCLUSRVLGVLG IKYFMKMLSSVSETLIFFFMGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTKMLASSGETIIFMFLGISAVD-PLIWTNNTAFVRLTLLFVSVFRAIGVVL VKYFFKMLAGSSETVIFMFLGISSTLSQHHFDLYFICATLFFCLIYRAIGTVV  *************  LTWFINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLSNSH-QMRNLFLTAIIT	346 358 350 333 261 431 399 411 403 387 314	
### ### ##############################	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYTTAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFFIISYLSYLISEMLSLSSILAITFCGICCKVYKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAAICGMLMKQYIKGNVTQAAANS   M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLIFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLIFCLIARVLGVLG IKYFKMLSSVSETLIFIFMCVSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTMKMLSSVSETLIFIFMSTVTGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTMKMLSSGSETIIFFHGUSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTMKMLASGAETIIFFHGUSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTKMLASGSETVIFMFLGISAVD-PLIWTWNTAFVRLALLFVSVFRAIGVVL VKYFKKMLASSSETVIFMFLGISTSSQH-HFDLYFICATLFFCLIYRAIGIVV  ***  ****************************	346 358 350 333 261 431 399 411 403 387 314	
M10	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYLTAEMFHLSGIMAITACAMTMKKYLENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQTSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFYLPYMAYLTAEMVSLSSILAITAICGMLMKQYIKGNVYQAAANS   MS  M9  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNW-TFVITTVILCLUSRVLGVLG IKYFKMMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCLUWRALGVFV IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCLUWRALSVFV IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCLUWRALSVFV IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNW-AFVCFTLAFCLUWRALSVFV IKYFMKMLASGAETIIFMFLGISAVD-PLIWTHNTAFVRLTLIFVSVFRAIGVVL VKYFTKMLASGSTVIFMFLGISTISSQH-HFDLYFICATLFFCLIVRAIGIVV  ** ** ** ** ** **  LTWFINKFRIVKLTPKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAITT LTFIINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLSNSH-QMRNLFLTAITT LTFIINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLSNSH-QMRNLFLTAITT LTFIINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLSNSH-QMRNLFLTAITT LTFIINKFRIVKLTKKDQFIIAYGGLRGAICFALVFLLPAAVFPRKKLFITAAIV LTYVINWFRTIPLTFKDQFIIAYGGLRGAICFALVFLLPAAVFPRKKLFITAAIV LTYVINWFRTIPLTFKDQFIIAYGGLRGAICFALVFLLPAAVFPRKKLFITAAIV	346 358 350 333 261 431 399 411 403 387 314	
NHE1	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE3 NHE3 ATNHE4 NHE1 NHE1 NHE NHE2 ATNHE4 NHE4 NHE4 NHE4 NHE4 NHE4	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMUSLSSIIAAIACGMLMKQYIKGNVTQAAANS   MS  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNWTFVISTLIFCLIARVLGVIG IKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV UKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFVSVFRAIGVVL VKYFKKMLAGSSETVIFMFLGISTISSQHHFDLYFICATLFFCLIYRAIGIVV  *********************************	346 358 350 333 261 431 399 411 403 387 314 486 453 466 453 442	
NHE1	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE3 NHE3 ATNHE4 NHE1 NHE1 NHE NHE2 ATNHE4 NHE4 NHE4 NHE4 NHE4 NHE4	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYTTAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAUTMKKYVEENVSQKSYTT KHORVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAIAICGMLMKQYIKGNVTQAAANS  M8  M9  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFKKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFFMGUSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGUSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGUSTVGKNHEWNWAFVCFTLAFCLIWRALGYFT VRYFMKMLSSVSETLIFIFMGUSTVGKNHEWNWAFVCFTLAFCLIWRALGYFT VRYFMKMLSSVSETLIFIFMGUSTVGKNHEWNWTFVISTLAFCLIWRALGYFT VRYFMKMLSSVSETLIFIFMGUSTVGKNHEWNWTFVISTLAFCLIWRALGYFT VRYFMKMLSSVSETLIFIFMGUSTVGKNHEWNAFVCFTLAFCLIWRALGYFT VRYFMKMLSVUGUNGSTVGKNHEWNTFVISTLAFCLIWRALGYFT VRYFMKHENTALITATATATATATATATATATATATATATATATATATA	346 358 350 333 261 431 399 411 403 387 314 486 453 466 453 442	
NHE VIFFTVFVGOMTIRPLVELLAVKKKESKPSINEEHHTEFLDHLLTGVEGVCGHY 508 NHE2 VIFFTVFILGITIRPLVEFLDVKRSNKKQAVSEEHHCFFDHVKTGIEDVCGHW 521 ATNHE4 VTYFTVFFGGITIGPLVRYLDVRKTNKKE-SINEEHHTLADHLKAGIEDVCGQW 512 NHE3 VVFFTVIFGGITIKPLVQWLKVKRSEHREPKLNEKHGRAFDHLLSALEDISGQI 497 ELEGAN WIYFTVYLGGITIKPLVQWLKVKKSEERDPTMVESVYNKYLDYMMSGVEDIAGQK 423  *** ** ** ** ** ** ** ** ** ** ** ** *	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE3 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYTTAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAAICGMLMKQYIKGNVTQAAANS   MS  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVLG IKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTMKMLSSVSETLIFIFMSVSTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTMKMLSSVSETLIFIFMSTVTGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTMKMLSSGSETIIFFHGUSTTVGKNHEWNW-AFVCFTLAFCLIWRALGYFV VRYTMKMLASGSETVIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VKYFKKMLSSVSETLIFIFMSTTSSQH-HFDLYFICATLFFCLIYRAIGIVV  *********************************	346 358 350 333 261 431 399 411 403 387 314 486 453 466 453 442	
NHE2         VIFFTVFILGITIRPLVEFLDVKRSNKKQQAVSEEHCRFFDHVKTGIEDVCGHW         521           ATNHE4         VTYFTVFFQGITIGPLVRYLDVRKTNKKE-SINEELHIRLMDHLKAGIEDVCGQW         512           NHE3         VVFFTVIFGGLTIKPLVQWLKVKRSEHREFKLNEKLHGRAFDHLLSALEDISGQI         497           ELEGAN         WIYFTVFLQGITIRPLVNFLKIKKKEERDPTMVESVYNKYLDYMMSGVEDIAGQK         423           NHE1         GHHHWKDKLNRFNKKYVKKCLIAGERSKEPQ-LIAFYHKMEMKQAILEVESGG         593           NHE2         GHYFWRDKFKKFDDKYLRKLLIRENQPKSSIVSLYKKLEIKHAIEMAETGM         572           ATNHE4         SHYQVRDKFKKFDDRYLRKLLIRENQPKSSIVSLYKKLEIKHAIEMAETGM         563           NHE2         GHYFURDKWANFDRRISKLLIMRQSAQKSRORILNVFHELINLKDAISYVTEGE         550           MELEGAN         GHYTFIENFERFMAKVIKPVLMRHQKRESFDASSIVRAYEKITLEDAIKLAK         475           **         *         *           NHE1         MGKIPSAVSTVSMQNIHPKALPAERILPASKKREEEIR         591           NHE2         ISTVPSFASINDCREEKI	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLGAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLFSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITGCGCKKYKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAIAICGMLMKQYIKGNVTQAAANS  *********  M8  IKYFLKMWSSVSETLIFFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFFLGVSTVAGPHAWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFFLGVSTVAGPHAWNWTFVITTVILCLUSKVLGVLG IKYFMKMLSSVSETLIFFHGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLSSVSETLIFFHGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLASSETIIFMFLGISAVD-PLIWTMNTAFVRLTLLFVSVFRAIGVUL VKYFFKMLAGSSETVIFMFLGLSTISQHHFDLYFICATLFFCLIYRAIGTVV  *********  LTWFINKFRIVKLTPKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKDQFIIAYGGLRGAIAFSLGYLLDKKHFPKKLFVTATLV QTWLLMRYRMVQLELIDQVWSYGGLRGAIAFSLGYLLDKKKFKLFVTATLV QTWLLMRYRMVQLELIDQVWSYGGLRGAIAYGLVVSIPAS-ITRKPMFITATIA  ********************************	346 358 350 333 261 431 399 411 403 387 314 486 458 442 368	
ATMHE4	NHE NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE2 ATNHE4 NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE2 ATNHE4 NHE3 ELEGAN NHE1 NHE3 ELEGAN NHE1	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYTTAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAAICGMLMKQYIKGNVTQAAANS   MS  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVLG IKYFKKMLSSVSETLIFIFMCVSTVGKNEEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSVSETLIFIFMCVSTVGKNEEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSGSETLIFIFMCVSTVGKNEEWNW-A-FVCFTLAFCLIWRALGYFV VRYTMKMLSSQSETLIFIFMCVSTVGKNEEWNW-A-FVCFTLAFCLIWRALGYFV VRYTMKMLSSOSTLIFIFMCVSTVGKNEEWNW-A-FVCFTLAFCLIWRALGYFV VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VKYFKKMLSSVSETLIFIFMCVSTVGKNEEWNW-A-FVCFTLAFCLIWRALGYFV VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFFCLIWRALGYFV VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFFCLIWRALGYFV VKYFTKMLAGGETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFFCLIWRALGYFV VRYTMKMLAFGLFGATAFSLGYLLDKKHFPMCDLFLTATIT LTFIINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTATIT LTFIINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTATIT LTFVINWFRTIPLITFKDQFIIAYGGLRGAICFALVFLLPAAVFPRKKLFVTATIV QTWLLMRYRMVQLEBLIDQVVWSYGGLRGAVFALVALLDGHKVKEKNLFVSTTII QCYILNRFRAKKFEMVDQFIMSYGGLRGAVAFALVALLDGHKVKENNLFVSTTII QCYILNRFRAKKFEMVDQFIMSYGGLRGATAYGLVVSIPAS-ITRKPMFITATIA  * * * * * * * * * * * * * * * * * * *	346 358 333 261 431 399 411 403 387 314 486 453 466 453 468	
MHE3	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE1 NHE1 NHE1 NHE1 NHE1 NHE1 NH	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYLTAEMFHLSGIMAITACAWTMKKYLENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAUTMKKYVEENVSQKSYTT KHYRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAIAICGMLMKQYIKGNVTQAAANS   M8  M9  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFKKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGUSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGUSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWTFVISTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWTFVISTLAFCLIWRALGYFV VRYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWTFVISTLAFCLIWRALGYFV VRYFMLAGGLAGALAFALVALLDGVKKKLFTATITA LTVNINMFRIPLTFKOOFTIAFGRAFALVALLDGNKVKKKLFVSTTIT QCYILMFFRAKKFEMVOOFTIMSYGGLRGAIAFGLVASLDGNKVKEKNLFVSTTIT QCYILMFFRAKKFEMVOOFTIMSYGGLRGAIAFGLVVSLPAS-ITRKPMFITATIA * * * * * * * * * * * * * * * * * * *	346 358 350 333 261 431 399 411 403 387 314 486 458 442 368 541 508	
***	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 NHE2 NHE2 NHE2 NHE3 NHE2 NHE3	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMLSLSSILAITACGULMKQYIKGNVTQAAANS   M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNWTFVISTLLFCLIARVLGVLG IKYFKKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFKKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRAIGVFV VKYFTKKMLASSETLIFFHGVSTVGKNHEWNWAFVCFTLAFCLIWRAIGVFV VKYFTKKMLASSETLIFFHGUSTDGHLAFULFULFVSUFFRAIGVVL VKYFTKKMLASSETLIFFLGISAVD-PLIWTWNTAFVRLTLLFYSVFRAIGVVL VKYFTKKMLASSETTIFFLGISAVD-PLIWTWNTAFVRLTLLFYSVFRAIGVVL VKYFTKKMLASSTVTIFFLGLISTISSQHHFDLYFLCATLFFCLIYRAIGIVV **********************************	346 350 333 261 431 399 411 403 387 314 486 458 442 368 541 508 521 512	
NHE1 GHHHWKDKLNRFNKKYVKKCLIAGERSKEPQ-LIAFYHKMEMKQAIELVESGG 593 NHE2 GHYHWKEKLNRFNKTYVKRWLIAGENFKEPE-LIAFYRKMELKQAIMMVESGQ 560 NHE2 GHNFWRDKFKKFDDKYLRKLLIRENQPKSSIVSLYKKLEIKHAIEMAETGM 572 ATNHE4 SHYQVRDKFKKFDHRYLRKILIRRNQPKSSIVSLYKKLEIKHAIEMAETGM 563 NHE3 GHNYLRDKWANFDRRFLSKLLMRQSAQKSRDRILNVFHELNLKDAISYVTEGE 550 ELEGAN GHYFFIENFERFNAKVIKPVLMRHQKRESFDASSIVRAYEKITLEDAIKLAK 475  NHE1 MGKIPSAVSTVSMQNIHPKALPAERILPASKDKEEEIR 632 NHE2 ISTVPSFASLNDCREEKI	HHE NHE NHE NHE NHE NHE NHE NHE NHE NHE	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMLYSLSSILAITACGCCKTYKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMLYSLSSILAITACGCMLMKQYIKGNVTQAAANS  **********  M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVLG IKYFLKMWSSVSETLIFIFMGVSTVCKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLSSVSETLIFIFMGUSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLASGAETIIFMFLGISAVD-PLIWTHNTAFVRLTLLFVSVFRAIGVLU VXYFFKMLAQSSETVIFMFLGISTISSQHHFDLYFICATLFFGLIYRAIGIVV  **********  LIWFINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLTFKDQFIIAYGGLRGAICFALVFLLPAAVFPRKKLFVTATLV QTWLLNYRMVQLELIDQVVMSYGGLRGAVAFALVALLDGNKVKEKNLFYSTTII QCYILNFRAKKFEMVDQFIMSYGGLRGAIAYGLVVSIPAS-ITKPMFTTATIA  *******  ********  ********  *******  ****	346 358 350 333 261 431 399 411 403 314 464 453 4658 442 368 541 508 521 512 512	
NHE	NHE NHE2 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMUSLSSIIAAIACGMLMKQYIKGNVTQAAANS   M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVIG IKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV UKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFVSVFRAIGVVL VKYFKKMLASSTVIFMFLGISTISSQHHFDLYFICATLFFCLIYRAIGIVV  *********************************	346 358 350 333 261 431 399 411 403 314 464 453 4658 442 368 541 508 521 512 512	
NHE	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMUSLSSIIAAIACGMLMKQYIKGNVTQAAANS   M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVIG IKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV UKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFVSVFRAIGVVL VKYFKKMLASSTVIFMFLGISTISSQHHFDLYFICATLFFCLIYRAIGIVV  *********************************	346 358 350 333 261 431 399 411 403 314 464 453 4658 442 368 541 508 521 512 512	
ATMHE4 SHYQVRDKFKKFDHRYLRKILIRRNÖPKSSIVSLYKKLEMKQAIRMAETGL 563  NHE3 GHNYLRDKWANFDRRFLSKILMRQSAQKSRDRILNVFHELNLKDAISYVTEGE 550  ELEGAN GHYFIENFERFMAKVIKPVLMRHQKRESFDASSIVRAYEKITLEDAIKLAK 475  NHE1 MGKIPSAVSTVSMQNIHPKALPAERILPASKDKEEEIR 632  NHE1 LPSVLPSTISMQNIQPRAIPR	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLISEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITACGULMKQYIKGNVTQAAANS   M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGVLG IKYFLKMWSSVSETLIFIFHGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV VXYFTKKMLASSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRAIGVFV VXYFTKKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFVSVFRAIGVVL VXYFTKKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFFCLIYRAIGIVV ** ** ** ** ** **  LITWFINKFRIVKLTKKOQFIVAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFINKFRIVKLTKKOQFIVAYGGLRGAIAFSLGYLLDRAVPPRKKLFITAIV LTVSVNNGFRTFPFSIKDQLIIFYSGVRGASFFSLAFILPLTLIFPRKKLFVTATLV QTWLLNYFRWVQLELIDQVVMSYGGLRGAIAFSLGYLLDGKVKKKFENLFVSTTII QCYILNFFRAKKFEMVDQFIMSYGCLRGAIAYGLVVSIPAS-ITKKPMFITATIA ** ** ** ***  M10  VIFFTVFVQGMTTRPLVDLLAVKKKQETKRSINEEHTTQFLDHLLTGIEDICGHY VIFFTVFTGGLTITBLVEFLDVKRSNKKQQAVSEEHCRFFDHVKTGIEDVCGHW VYFFTVFTGGLTITBLVEFLDVKRSNKKQCAVSEEHCRFFDHVKTGGIEDVCGHW VYFFTVFTGGLTITBLVWFLKVKKKEERPDTMVESVYNKYLDYMMSGVEDIAGGK *** ** *** *** *** *** *** *** *** ***	346 358 350 333 261 431 399 411 403 387 314 486 458 442 368 521 593 593	
NHE3	NHE NHE2	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITACGCCKTYKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAIAICGMLMKQYIKGNVTQAAANS  **********  M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFMGVSTVCKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTKMLASSGETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTKMLASSETLIFIFMGUSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTKMLASGAETIIFMFLGISAVD-PLIWTNNTAFVRLTLLFVSVFRAIGVVL  **********  LIWFINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIPLTFKDQFIIAYGGLRGAIAFSLGYLLDLAVKKKENLFYSTTII QCYILNRFRAKKFEMVDQFIMSYGGLRGAIAYGLVVSIPAS-ITRKPMFITATIA  ********  **********  **********	346 358 333 261 431 399 411 403 314 486 453 4658 442 368 541 5521 5122 593 593 560	
### ##################################	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 NHE3 ELEGAN  NHE1 NHE1 NHE2 NHE1 NHE2 NHE1 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYTTAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMUSLSSIIAAIACGMLMKQYIKGNVTQAAANS   M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFHKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCLIWRALGYFV UKYFMKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCCJWRAISVFT VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VKYFTKMLASGSETVIFMFLGISTISSQHHFDLYFICATLFFCLIYRAIGIVV  *** ** ** ** **  LTWFINKFRIVKLTPKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAITT LTFYINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAITT LTFYINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLDKKHFPKKLFVTATLV QTWLLNTXFRMVQLEILDQVWSYGGLRGAVFFLVALLDGKKVKENLFVSTTII QCYILNTFRAKKFEMVDQFIMSYGGLRGAVFFLVALLDGKKVKENLFVSTTII QCYILNTFRAKKFEMVDQFIMSYGGLRGAVFFLVALLDGKKVKENLFVSTTII  VIFFTVFVQGMTIRPLVDLLAVKKKQETKRSINEEHHTQFLDHLLTGIEDICGHY VIFFTVFVQGMTIRPLVBLLAVKKKKQETKRSINEEHHTGFLDHLLTGUEDVCGW VVFFTVFIGGITIGPLVRYLDVKSNKKQQAVSEEHHREFFDHNKTGIEDVCGW VVFFTVFIGGITIGPLVRYLDVKSNKKQGVSSEBIAFEFFHVLRSGIEDVCGW VVFFTVFIGGITIGPLVRYLDVKSNKKQGVSSEBIAFFFFHLIRLMPHLKAGIEDVCGW VVFFTVFTGGTTIGPLVRYLDVKSNKKQGVSSEBIAFFFHLARIFTHLSAIDISGG MYYFTVFLQGITIGPLVRYLDVKSNKKQETKRSINEEHHTGFLDHLLAGGEDVCGW VVFFTVFTGGTTIGPLVRYLDVKSNKKQETKRSINEEHHTGFLDHLLAGGEDVCGW VVFFTVFTGGTTIGPLVRYLDVKSNKKQETKRSINEEHHTGFLDHLLAGGEDVCGW VVFFTVFTGGTTIGPLVRYLDVKSNKKQETKRSINEEHHTGFLDHLLAGGEDVCGW VVFFTVFTGGTTIGPLVRYLDVKSNKKQETKRSINEEHHTGFLDHLLAGGEDVCGW VVFFTVFTGGTTIGPLVRYLDVKSTNKKE-SINEELHTRLMDHLKAGIEDVCGW VVFFTVFTGGTTIGPLVRYLDVKSTNKKE-SINEELHTRLMDHLKAGIEDVCGW VYFTVFTGGTTIGPLVRYLDVKSTNKKE-SINEELHTRLMDHLKAGIEDVCGW VYFTVFTGGTTIGPLVRYLDVKSTNKKE-SINEELHTRLMDHLKAGIEDVCGGW MYTYTTYLGGLTTRPLVKFLLKKKEERPDFTMVESCYNKYLDYMMSGVEDIAGGK ***********************************	346 358 350 333 261 431 399 411 403 387 314 486 458 458 458 458 458 458 458 458 458 458	
*	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE1 NHE1 NHE2 ATNHE4 NHE3 NHE1 NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITACGICCKKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITACGCMLMKQYIKGNVTQAAANS  **********  M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNWTFVISTLLFCLIARVLGVLG IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTKMALSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTKMALASSETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL  **********  LIWFINKFRIVKLTPKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFTTAIIT LTFYINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCKLFYTATLV QTWLLMRYRWYQLELIDQVWSYGGLRGAVAFALVALLDGNKVKEKNLFYSTTII QCYILNRYRWYQLELIDQVWSYGGLRGAVAFALVALLDGNKVKEKNLFYSTTII QCYILNRFRAKKFEMVDQFIMSYGGLRGAIAYGLVVSIPAS-ITRKPMFITATIA  ***  ***  ***  ***  ***  ***  **	431 359 411 431 399 411 403 314 486 458 442 368 521 508 521 512 593 560 576 576 576 576 576 576 576 576 576 576	
NHE1 MGKIPSAVSTVSMQNIHPKALPAERILPALSKDKEEEIR 632 NHE LPSVLP-STISMQNIQPRAIPRSKREEEIR 591 NHE2 ISTVPSFASLNDCREEKI	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCQKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMUSLSSIIAAIACGMLMKQYIKGNVTQAAANS   MS  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGULG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLIFCLIARVLGULG IKYFLKMWSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRAIGVFV VKYFTKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFVSVFRAIGVVL VKYFTKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFFCLIYRAIGIVV ***********  LITWFINKFRIVKLTKKOOFIVAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAITI LTRVINWFRTIPLTFKOOFITAYGGLRGAICFALVFLLPAAVPPRKKLFITAAIV LFYSNQFRTFPFSIKOQLIIFYSGVRGASFFSLAFLLPLTLFPRKKLFVTATLV QTWLLNRYRMVQLELIDQVVMSYGGLRGAIAFSLGYLLDGKKVKEKNLFVSTTII QCYILNFFRAKKFEMVDCFIMSYGCLRGAIAFSLGYLLDGKKVKEKNLFVSTTII QCYILNFFRAKKFEMVDCFIMSYGCLRGAIAYGLVVSIPAS-ITRKPMFITATIA ********  M10  VIFFTVFVQGMTIRPLVDLLAVKKKQETKRSINEEIHTQFLDHLLTGIEDICGHY VIFFTVFTGGTTIRPLVFLLAVKKKKESKFSINEEIHTGFLDHLLTGUECVGHW VTYFTVFTGGTTIRPLVFLLAVKKKKESKFSINEEHTRIMDHLKAGIEDVCGW VTYFTVFTGGTTIRPLVFLKLAVKKKESKFSINEEHTRIMDHLKAGIEDVCGW VTYFTVFTGGTTIRPLVFLKYLKVKKRERHFPKLNEKLHGAFFDHVKTSIEDVCGW VTYFTVFTGGTTIRPLVFLKYLKVKKRERHFPFLNEKLHGAFDHILSAIEDISGGI WIYFFVFLGGTTIRPLVNFLKKKKRERFPFLNEKLHGAFFDHVTSIEDVCGW VTYFTVFTGGTTIRPLVNFLKKKKERFPFLNEKLHGAFFDHVTSIEDVCGW VTYFTVFTGGTTIRPLVRFLKYKKKERFPFLNEKLHGAFFDHVTSIEDVCGGW GHHWWIDKLNRFNKKYVKKCLIAGERSKEPQ-LIAFYRKMELKQAIMMVESGG GHYHWRDKKRKFDHRYLKKLLIRENQPKSSIVSLYKKLEHKQAIEMAETGL SHYVRDKFKKFDDKYLRKILIRENQPKS-SIVSLYKKLEHKQAIEMAETGL SHYVRDKFKKFDHRYLKKILTRENGPKSSIVSLYKKLEHKQAIEMAETGL SHYVRDKKKKFDHRYLKKILTRENGPKSRDRILNVHHELLALBAIEDISCHEGHNYLRGAAFGA-S-RDRILNVHHELLALBAIENSAIESCE GHYHWEDKWANFDFRISKLLURGSAGKS-R-RDRILNVHHELLALBAIENGABFGL SHNYURDKFKKFDHRYLKRILTRENGPKSRDRILNVHHELNADAIESVTEEG GHYHMEDKWANFDFISKLLURGSAGK	346 358 333 261 431 399 411 403 387 314 486 458 458 458 541 508 512 423 423 568 572 563 565 565	
NHE LPSVLPSTISMQNIQPRAIPRVSKKREEEIR 591 NHE2 ISTVPSFASLNDCREKI	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYLTAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAAICGMLMKQYIKGNVTQAAANS   MS  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVLG IKYFKKMLSSVSETLIFIFMCVSTVGKNHEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSVSETLIFIFMCVSTVGKNHEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSVSETLIFIFMCSTVGKNHEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VKYFKKMLSSVSETLIFIFMCSTVGKNHEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VKYFKKMLSSVSETLIFIFMCSTVGKNHEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFFCLIWRALGYFV VXFTKMLAGSETVIFMFLGISAVD-PLIWTWNTAFVRLTLLFFCLIWRALGYFV VXFTKMLAGGETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFFCLIWRALGYVL VXYFTKMLAGGETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFFCLIWRALGIVV VTYTINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT QCYILNRFRAKKFEMVDQFIMSYGGLRGAVFALVALLDGNKVKKRLFVSTTIV QCYILNRFRAKKFEMVDQFIMSYGGLRGAVFALVALLDGNKVKKRLFVSTTIV QCYILNRFRAKKFEMVDQFIMSYGGLRGAVAFALVALLDGNKVKKRLFVSTTIV VTYFTVFFCGCITIGPLVWFLLAVKKKKESKPSINEEHHTGFLDHLLTGLEDICGHY VTYFTVFFCGCITIGPLVWFLLAVKKKKESKPSINEEHHTGFLDHLLTGLEDICGHY VTYFTVFFCGCITIGPLVWFLLAVKKKKESKPSINEEHHTGFLDHLLTGAEIEDICGHY VTYFTVFFCGCITIGPLVWFLVKKKKERFPKLEKKHGRAPHILSAIEDISGGI WYYFTVFFCGCITIGPLVWFLVKKKERFPKLEKKHGRAPHILSAIEDISGGI WYYFTVFFCGCITIGPLVWFLVKKCLIAGERSKEPQ-LIAFYKMEMKQAIELVESGG GHNFWKDKLNRFNKKYVKKCLIAGERSKEPQ-LIAFYRKMEMKQAIELVESGG GHNFWKDKLNRFNKKYVKKCLIAGERSKEPLIAFYRKMEKKQAIENVESGG GHNFWKDKLNRFNKKYVKKCLIAGERSKEPLIAFYRKMELKQAIMVESGC GHNFWKDKLNRFNKYVKKCLIAGERSKEPR-LIAFYRKMELKQAIMVESGC GHNFWKDKLNRFNKYVKKCLIAGERSKE-SLVSLYKKLEIKALEMAFGG GHYFTLANGVKFKFDHRYLLRKLLIRRNQPKSSLVSL	346 358 333 261 431 399 411 403 387 314 486 458 458 458 541 508 512 423 423 568 572 563 565 565	
NHE2 ISTVPSFASLNDCREEKI	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYTTAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSIIAIAICGMLMKQYIKGNVTQAAANS   MS  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNW-TFVISTLLFCLIARVLGVIG IKYFKKMLSSVSETLIFIFMCVSTYGKNEEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSVSETLIFIFMCVSTYGKNEEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSGSETLIFIFMCVSTYGKNEEWNW-A-TFVISTLLFVGLWRAISVFT VRYTMKMLSSGSETLIFIFMCVSTYGKNEEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSGSETLIFIFMCVSTYGKNEEWNW-A-PVCFTLAFCLIWRALGYFV VRYTMKMLSSGSETLIFIFMCVSTYGKNEEWNW-A-TFVISTLLFVGLWRAISVFT VRYTMKMLSSGSETLIFIFMCVSTYGKNEEWNW-A-TFVISTLLFFCLIWRAIGVFV VKYFTKMLSSVSETLIFIFMCVSTYGKNEEWNW-A-TFVLFTLAFCLIWRALGYFV VKYFTKMLSSVSETLIFIFMCVSTYGKNEEWNW-A-TFVLFTLAFCLIWRAIGUFV VYFTINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLIFFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT QCYILNRFRAKKFEMVDQFIMSYGGLRGAVFALVALLDGRKVKKRNLTVSTTII QCYILNRFRAKKFEMVDQFIMSYGGLRGAVFALVALLDGRKVKKRNLTVSTTII QCYILNRFRAKKFEMVDQFIMSYGGLRGAVFALVALLDGRKVKKNLTVSTTII VTFTVFVQGMTIRPLVBLLAVKKKKESKFSINEEHHTGFLDHLLTGIEDICGHY VIFFTVFTLGLITIRPLVFFLDVKRSNKKQQAVSBEHHCFFFDHVKTGIEDVCGHW VYFFTVFTQGITIGPLVRYLDVKKTNKKE-SINEELHIRLMDHLKAGIEDVCGHW VYFFTVFTQGITIGPLVRYLDVKKTNKKE-SINEELHIRLMDHLKAGIEDVCGHW VYFFTVFTQGITIGPLVRYLDVKKNKEERFPHVKEKLHGRAFDHILSAIEDISGI MYYFTVFLQGITIRPLVVRLUVKRNEKACHFKE-PE-LIAFYRKMEMKQAIELVESGG GHYHWKEKLNRFNKKYVKKCLIAGERSKEPQ-LIAFYHKMEMKQAIELVESGG GHYHWKEKLNRFNKTYVKRWLLIAGENFKEPE-LIAFYRKMELKQAIMNVESGQ GHNFWKDKKKFRDRKYYKKCLIAGERSKEPR-LIAFYRKMELKQAIMAESGQ GHNFWKDKKKFRDRKYYKKCLIAGERSKEPR-LIAFYRKMELKQAIMAESGQ GHNFWRDKFKKFDDRYLAKILTRNDQNSSIVSLYKKLEIKHADAISVVTEGG GHNYLRDKWANFDRFLSKLLHRNDQNS-SIVSLYKKLEIKHADAISVVTEGG GHYTFURDKFRFNAKVIKFULM	346 358 333 261 431 399 411 403 387 314 486 458 458 458 541 508 512 423 423 568 572 563 565 565	
ATHHE4 LSSVASPTPYQSERIQGIKRLSPEDVESMR 593 NHE3 RRGSLAFIRSPSTDNMVNVDFSTPRPSTVEASVSYLLRESASAVCLDMQSLEQRR 605	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITACGULMKQYIKGNVTQAAANS  **********  M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAKHEWNWAFVCFTLAFCQIWFALGSVFT VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VKYFTKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFYSVFRAIGVVL VKYFTKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFYSVFRAIGVVL VKYFTKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFYSVFRAIGVVL VXYFTKMLASGAETIIFMFLGISATSSQHHFDLYFICATLFFCLIYRAIGIVV  *********  LIWFINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINWFRTIPLTFKDQFIIAYGGLRGAICFALVFLLPAAVPPRKKLFYTATLV QTWLLNRYRMVQLELIDQVVMSYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIVKLTFKDQFIIAYGGLRGAICFALVFLLPAAVPPRKKLFYTATLV QTWLLNRYRMVQLELIDQVVMSYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFTTYTHUFTGUGTIRFLVGVLKKKKGETKRSINEEHTQFLDHLLTGIEDICGHY VIFFTVFTUGGTITRPLVELLAVKKKQETKRSINEEHTQFLDHLLTGIEDICGHY VIFFTVFTGGTITIPLVWLKYMKKKSEKPRSHEEHTAFLDHLLTGIEDICGHY VIFFTVFTGGTITIPLVWLKYMKKKSEKPRSHEEHTGFLDHLLTGLEDICGGK  *********  GHHHWKDKLNRFNKTYVKKCLIAGERSKEPQ-LIAFYHKMEMKQAIENAETGU GHYYDKFKKFFDNKYLKYKKLLIRROPKSSIVSLYKKLEKKGAIEMAETGU GHYYDKFKKFFDNKYLVKRULLARGAGKS-SIVSLYKKLEHKAIEMAETGU GHYYDKOKFKKFDDKYLRKLLTRROPKS-SIVSLYKKLEHKAIEMAETGU GHYYDKOKFKKFDDKYLKKLLTRROPKS-SIVSLYKKLEHKAIEMAETGU GHYYDKOKFKKFDDKYLKKLLTRROPKS-SS-IVSLYKKLEHKAIEMAETGU GHYYDROKFKFFDNKYLKYUKRHGKRESFDASSIVRAYEKITLEDAIKLAK  *********************************	431 359 411 431 399 411 403 314 486 453 442 368 521 508 521 508 521 508 521 508 509 509 509 509 509 609 509 609 609 609 609 609 609 609 609 609 6	
NHE3 RRGSLAFIRSPSTDNMVNVDFSTPRPSTVEASVSYLLRESASAVCLDMQSLEQRR 605	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE1 NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYLTAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMUSLSSIIAIAICGMLMKQYIKGNVTQAAANS   MS  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGPHAWNWTFVISTLLFCLIARVLGVIG IKYFHKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV UKYFHKMLSSVSETLIFIFMCVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTMKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VKYFTKMLASGSETVIFMFLGISTISSQHHFDLYFICATLFFCLIYRAIGIVV  *** ** ** ** **  LTWFINKFRIVKLTPKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAITT LTFYINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAITT LTFYINKFRIVKLTKKDQFIVAYGGLRGAIAFSLGYLLDAAVFPRKKLFVTATIV QTWLLMRYRMVQLELIDQVWSYGGLRGAVFALVALLDGKKVKENLFVSTTII QCYILNRFRAKKFEMVDGFIMSYGGLRGAVFALVALLDGKKVKENLFVSTTII QCYILNRFRAKKFEMVDGFIMSYGGLRGAVFALVALLDGKKVKENLFVSTTII QCYILNRFRAKKFEMVDGFIMSYGGLRGAVFALVALLDGKKVKENLFVSTTII QCYILNRFRAKKFEMVDGFIMSYGGLRGAVFALVALLDGKKVKENLFVSTTII QCYILNRFRAKKFEMVDGFIMSYGGLRGAVFALVALLDGKKVKENLFVSTTII QCYILNRFRAKKFEMVDGFIMSYGGLRGAVFALVALLDGKKVKENLFVSTTII QCYILNRFRAKKFEMVDGFIMSYGGLRGAVFALVALLDGKKVKENLFVSTTII QCYILNRFRAKKFEMVDGFIMSYGGLRGAVFALVALLDGKKVCHUNTYFTUFUGGLTIRPLVFLLAVKKKKESKFSINEEIHTGFLDHLLTGIEDLCGHY VIFFTUFVQGMTIRPLVBLLAVKKKKESKFSINEEHTGFLDHLLTGIEDLCGHY VIFFTUFVQGMTIRPLVBLLAVKKKKESKFSINEEHTGFLDHLLTGIEDLCGHY VIFFTUFVGGTTIGPLVRYLDVKTNKKE-SINEEHTRLMDHLKAGIEDVCGW VVFFTVIFGGTTIGPLVRYLDVKTNKKE-SINEEHTRLMDHLKAGIEDVCGW VVFFTVIFGGTTIGPLVRYLDVKTNKKE-SINEEHTRLMDHLKAGIEDVCGW VTYFTVFQGTTIGPLVRYLDVKTNKKE-SINEEHTRLMDHLKAGIEDVCGW HYFTVFLGGTTRPLVVGLKKKEREFPHNESSCH-PQ-LIAFYHKMEMKQAIELUCSGG GHYHWKEKLNRFNKYVKKCLLAGERSKEPQ-LIAFYHKMEMKQAIEMLSGG GHYHWKEKLNRFNKYVKKCLLAGERSKEPQ-LIAFYHKMEMKQAIEMAETGL GHNYLBOKKNANFFDRFISKLLMRGSAKKS-S-DIVSLYKKLEIKHAIEMAETGL GHYLBOKANFTORDASVSTEGG GHYFHRDKKYNKYLDLMRGSAKKS-RDBILNYHELNLKDAISVYTEGG GHYFHRDKKYNSWOLDRAIP-RL	346 358 333 261 431 399 411 403 387 314 486 458 458 458 458 458 458 458 458 458 458	
	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITACGCCKTYKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMVSLSSILAITACGCMLMKQYIKGNVTQAAANS  **********  M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVLG IKYFMKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTKMLASSGETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCQIWRAISVFT VRYTKMLASSAETLIFMFLGISAVD-PLIWTNNTAFVRLTLLFVSVFRAIGVVL VXYFFKMLAGSSETVIFMFLGISATD-PLIWTNNTAFVRLTLIFFCLIYRAIGTVV  *********  LTWFINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFIINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFVINWFRTIPLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIVKLTFKDQFIIAYGGLRGAIAFSLGYLLDKKHFPMCDLFLTAIIT LTFYINKFRIVKLTKKDQFIIAYGGLRGAIAFSLGYLLDLAGKKVKENLFYSTTII QCYILNRFRAKKFEMVDQFIMSYGGLRGAIAYGLVVSIPAS-ITRKPMFITATIA  ***********  M10  VIFFTVFVQGMTIRPLVELLAVKKKKESKFSINEEHTQFLDHLLTGIEDICGHY VIFFTVFTGGLTITRPLVFLYBLLAVKKKKESKFSINEEHTGFLDHLKTGIEDVCGGW VYFFTVFTGGGLTIGPLVFLYBLLAVKKKKESKFSINEEHTGFLDHLKGAIEDVCGGW VYFFTVFTGGGTTIGPLVFLYBLKKKKEERDPTMVESVYNKYLDYMMSGVEDIAGGK  **********************************	431 359 411 431 387 314 486 458 4458 4458 4423 5512 497 423 560 570 570 570 570 570 570 570 570 570 57	
	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMUSLSSILAITACGULMKQYIKGNVTQAAANS   M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFKKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFKKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRAIGVFV VXYFTKKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VXYFTKKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFFCLIYRAIGIVV  *********************************	431 358 333 261 431 399 411 403 314 468 453 468 442 368 5418 521 512 572 423 593 475 632 632 632 632 632 632 633 633 633 633	
	NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE2 ATNHE4 NHE3 ELEGAN  NHE1 NHE NHE3 ELEGAN  NHE1 NHE1 NHE2 ATNHE4 NHE3 ELEGAN	AHIRVIEPLFVFLYSYMAYLSAELFHLSGIMALIASGVVMRPYVEANISHKSHTT SHTRVIEPLFVFLYSYMAYLSSEMFHLSGIMALIACGVVMRPYVEANISHKSHTT HNIRVIEPLFVFLYSYLSYITAEMFHLSGIMAITACAWTMKKYVEENVSQKSYTT QNISAIEPLIVFMFSYLSYLAAETLYLSGILAITACAVTMKKYVEENVSQKSYTT KHVRVIEPGFVFIISYLSYLTSEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMLSLSSILAITFCGICCKYVKANISEQSATT YDVRILAPVFIFVLPYMAYLTAEMUSLSSILAITACGULMKQYIKGNVTQAAANS   M8  IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFLKMWSSVSETLIFIFLGVSTVAGSHHWNWTFVISTLLFCLIARVLGVIG IKYFKKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRALGVFV IKYFKKMLSSVSETLIFIFMGVSTVGKNHEWNWAFVCFTLAFCLIWRAIGVFV VXYFTKKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLLFVSVFRAIGVVL VXYFTKKMLASGAETIIFMFLGISAVD-PLIWTWNTAFVRLTLIFFCLIYRAIGIVV  *********************************	431 359 411 431 387 314 486 458 4458 4458 4458 4458 4458 456 458 445 457 423 560 560 560 560 560 560 560 560 560 560	Fig. 4. Legend on next pa

RNHE1 BNHE RNHE2 RATNHE4 RNHE3 CELEGAN	KILRNNLQKTRQRLRSYNRHTLVADPYEEAWNQMLLRRQKA RILRANLQNNKQKMRSRSYSRHTLFDADEEDNVSEVRLRTYKN EILSRNLYQIRQRTLSYNRHNLTADTSERQAKEILIRRHS DILTRNNYQVRQRTLSYNKYNLKPQTSEKQAKEILIRRQNT RSVRDAEDVITHHTLQQYLYKPRQEYKHL-YSRHVLSPSEDEKQNKEIFHRTMRKVKNNIQNKRLERIKSKGRV	673 634 643 634 659 504
RNHE1 BNHE RNHE2 RATNHE4 RNHE3 CELEGAN	RQLEQKINNYLTVP-AHKLDS-PTMSRARIGSDPLAYEPK EMERRYS-VMERRNSHYLTVP-ANRESPRGVRRVRFESDNQVFSAD LRESIRKDN-SLNRERRASTSTSRYLSLPKNTKLPEKLQKKKNISNADGDSSDSE LRESLRKGQ-SLPWVKPACTKNFRYLSFPYSNPQPARRGARAAEST RLESFKSAKLGLGQSKKATKH	711 679 697 679 701 512
RNHE1 BNHE RNHE2 RATNHE4 RNHE3 CELEGAN	ADLPVITIDPASPQSPESVDLV-NEELKGKVLGLSREPRVAEEA S-FPTVHFEQPSPPSTPDAVSL ADAGTTVLINLQFRARRFLEEPFSKKASQAYKMEWKNEVDAGSGQGGPSPPAAPRS GNPCCWLHFL	754 700 752 690 750 553
RNHE1 BNHE RNHE2 RATNHE4 RNHE3 CELEGAN	AEEDEDEGGIVMRPK-EPSSPGTDDVFSPAPSDSPSSQRMQEEEEEEVPKRPSLKADIEGPRGNASDNNQGELDYQRLA KEGGTQTPAVLRQPLLSKDQGREDSLTEGGRPKPPPRLV	793 738 791 712 805 597
RNHE1 BNHE RNHE2 RATNHE4 RNHE3 CELEGAN	R-CLSDPGPHPEPGEGEPFIPKGQ 816 R-CLSDPGPNKDKEDDDPFMSC 759 R-RASEPGNRKSRLGSDKP 809 C-RNLN	

Fig. 4. Deduced amino acid composition and alignment of amino acid sequences of several members of the eukaryotic Na<sup>+</sup>/H<sup>+</sup> exchanger gene family. (\*) Indicates identically conserved residues among the sequences shown. Residues that are conserved in five of the isoforms shown are indicated by a dot (·). Sequences shown are rabbit NHE1 (RNHE1, ref 75), rabbit NHE2 (RNHE2, ref 74), rabbit NHE3 (RNHE3, ref 73), rat NHE4 (RATNHE4, ref 59), trout red blood cell BNHE (BHNE, ref 7), and Na<sup>+</sup>/H<sup>+</sup> exchanger from C. elegans (CELEGAN, ref 49). Note that the entire N-terminus of C. elegans has not been cloned.

modifier site, are regulated by growth factors and protein kinases, and are inhibited by the diuretic amiloride. Differences as well as similarities in regulation have been identified.

#### KINETICS

NHE1, NHE2, and NHE3 have been studied when stably transfected [47, 67, 73, 75, 77]. The expression system used for these functional studies has primarily been the PS120 fibroblast cell line. The cloned exchangers show similar kinetic characteristics when undergoing Na<sup>+</sup>-dependent pH recovery following an acid load [3, 8], although the exchangers differ in their response to growth factors and phorbol esters. For all three expressed exchangers, Na<sup>+</sup>/H<sup>+</sup> exchange [46] is entirely inhibited by amiloride and/or 5'-amino substituted amiloride analogues. The kinetics for external Na<sup>+</sup> follows a classical Michaelis-Menten model with a  $K_m^{\rm Na^+} \sim 16$  mM and with a Hill coefficient of 1, suggesting that there is a single binding site for external Na<sup>+</sup> [46].

The kinetics with respect to internal H<sup>+</sup> are also similar for the three exchangers with all three deviating from the hyperbolic response expected with Michaelis-Menten kinetics and all having a Hill coefficient of between 2–3 [46]. The data describing the effect of intracellular H<sup>+</sup> best fit an allosteric model

with at least two independent binding sites for H<sup>+</sup> [46]. In addition to the internal H<sup>+</sup> transport site, there is thought to be an internal modifier site for intracellular H<sup>+</sup>, which can regulate the activity of the exchanger [3]. This modifier site is located in the N-terminal domain as its effects are still seen in truncated antiporters in which almost the entire Cterminal cytoplasmic domain has been deleted (this has been determined for NHE1, NHE2, and NHE3) ([77]; S. Levine, C. Yun, M. Donowitz, M. Tse, unpublished data). Of note is that this contradicts some plasma membrane vesicle transport studies which claimed that several intestinal Na<sup>+</sup>/H<sup>+</sup> exchangers lacked an internal modifier site, based on the demonstration of a nonallosteric, Michaelis-Menten relationship between internal H<sup>+</sup> and rate of Na<sup>+</sup>/H<sup>+</sup> exchange in colonic brush border and ileal brush border and basolateral membranes [39, 62]. While these results may predict the presence of additional epithelial specific NHE isoforms, they also may represent an artifact of either the method of preparing the vesicles or be due to the difficulty of performing vesicle studies with a sufficient number of intracellular pHs to adequately define the relationship between pH and rate of Na<sup>+</sup>/H<sup>+</sup> exchange. Of note is that a modifier site was not demonstrated in rabbit ileal basolateral membranes which are known to contain NHE1 [39]. This supports the difficulty of demonstrating a modifier site using vesicles; and a modifier site has been demonstrated with slightly different techniques in human small intestinal apical membranes (K. Ramaswamy, privileged communication).

Functional Domains: Role of the N-Terminal Domain and C-terminal Cytoplasmic Domain

To obtain insight into molecular mechanisms of second messenger regulation of the Na<sup>+</sup>/H<sup>+</sup> exchanger, Wakabayashi et al. [77] constructed a set of deletions within the cytoplasmic carboxyl-terminus of human NHE1 and stably expressed the truncated cDNAs in PS120 fibroblasts. A number of conclusions can be drawn from their studies: (i) almost complete deletion of the C-terminus (approximately 15 amino acids from the end of the putative last membrane spanning domain) retains amiloride-sensitive Na<sup>+</sup>/H<sup>+</sup> exchange activity, indicating that the cytoplasmic domain is not essential for ion transport and that the N-terminal portion can be inserted into the plasma membrane and carry out transport. However, this truncation transported at a much slower rate than did the wild type exchangers. Not yet known is the relative amount of each exchanger expressed in the plasma membrane. (ii) The H<sup>+</sup> modifier site must be located within the N-terminal domain since the allosteric activation of the exchanger by internal H<sup>+</sup> is preserved after almost complete removal of the cytoplasmic C-terminus. Of note, the truncated NHE1 is turned off at a lower pH than is the wild type indicating a change in set point of the exchanger. (iii) Presence of a negative element that "downregulates" the exchanger at the C-terminal portion of the long intracytoplasmic-end is suggested. The latter is based on the observation that a small C-terminal deletion of NHE1 (removing the last 117 amino acids) exhibited higher activity than the wild type, whereas further deletions led to a decrease in activity. However, these measurements were done using transiently transfected cells and activity was normalized to the expression of a reporter gene and not to the amount of Na+/H+ exchanger protein expressed. (iv) In NHE1 the cytoplasmic region between amino acid 566 and 635 is required for second messenger regulation since deletion of this region abolished response to growth factors, thrombin, and second messengers. There are eight serines in this region. Deletion of each individually failed to eliminate C kinase regulation of the Na<sup>+</sup>/H<sup>+</sup> exchange rate. Thus, it is likely that multiple serines are phosphorylated [68].

The separation of the Na+/H+ exchanger into

a part of the molecule which has multiple membrane spanning domains and a portion of the molecule which is cytoplasmic is found in another epithelial neutral ion exchange protein, the Cl<sup>-</sup>/HCO<sub>2</sub> exchange gene family, which is related to the red blood cell Band 3 [40]. The anion exchanger gene family also has a conserved domain which is hydrophobic and is thought to be the part of the protein involved in ion movement and a long intracellular domain. The order is reversed in comparison with the Na<sup>+</sup>/H<sup>+</sup> exchanger gene family—in the anion exchanger, the C-terminus contains the hydrophobic domains. Of note, it has not vet been established that the anion exchanger is a phosphoprotein or is regulated by phosphorylation and thus it is not clear if there is also a functional analogy with the parts of the Na<sup>+</sup>/H<sup>+</sup> exchanger.

## Functional Domains: Amiloride Binding Site

The diuretic amiloride and its 5'-amino substituted analogues are potent inhibitors of the Na<sup>+</sup>/H<sup>+</sup> exchanger and block the exchanger by competing with Na+ for the external Na+ binding site [reviewed in 4]. There are multiple types of data which support that amiloride binds to the outside of the Na<sup>+</sup>/H<sup>+</sup> exchanger, including that amiloride inside red blood cell plasma membrane (ghosts) does not duplicate the effect of extracellular amiloride [32]. Extracellular amiloride is a competitive inhibitor of external Na<sup>+</sup> [4]. Amiloride seems to act by binding to the N-terminal part of the protein. Almost complete removal of the C-terminal 300 amino acids of NHE1 produces a protein, which is amiloride sensitive and has similar sensitivity to amiloride and a 5'-amino substituted amiloride analogue compared to the wild type Na<sup>+</sup>/H<sup>+</sup> exchanger [19, 77]. Of note is that deglycosylating NHE1 did not alter sensitivity to methylpropyl amiloride, indicating an independence of amiloride binding from glycosylation in NHE1. The cloned NHE isoforms have different sensitivities to amiloride and its 5'-amino substituted analogues. NHE1 is sensitive to amiloride and to 5'amino substituted analogues; NHE3 is resistant to both; while NHE2 is sensitive to amiloride and resistant to 5'-amino substituted analogues.

The first hints of which part of the Na<sup>+</sup>/H<sup>+</sup> exchanger contains the amiloride binding site implicate the fourth transmembrane helix (Table 2). The basis for this conclusion is the result of detection of amiloride-resistant Na<sup>+</sup>/H<sup>+</sup> exchanger clones [28]; sequencing their cDNAs [19]; comparing their amino acid composition and amiloride and methylpropylamiloride sensitivity with those of several

**Table 2.** Comparison of amino acid composition of NHE1 and NHE2 in the area of the putative fourth membrane spanning domain which appears to be involved in determining sensitivity of the Na<sup>+</sup>/H<sup>+</sup> exchanger isoform to amiloride and 5'-amino substituted amiloride.

cDNA	Amino acid sequence	IC <sub>50</sub> (Amiloride) μΜ	$IC_{50}$ (MPA) $\mu_{M}$	IC <sub>50</sub> (EIPA) μΜ
NHE1	VFFLFL	3	0.05	<u></u>
NHE1 → AR300	V	15	1.5	
NHE1 → NHE2	VFFLYL	3	0.05	
NHE1 → NHE3	V F F <u>F</u> <u>Y</u> L	15	1	
NHE1 → NHE4	V <u>Y</u> F L <u>Y</u> L	100	1	
NHE2	VFFLYL	1		0.5
NHE2 → AR300	V F F <u>F</u> <u>F</u> L	10		5
NHE2 → NHE1	V	1		0.3
NHE2 → NHE3	V F F <u>F</u> Y L	4		10

Point mutations were made in NHE1 (top) and NHE2 (bottom) to mimic the amino acid composition in comparable areas in NHE1, 2, 3, 4, and AR300. Underlined amino acids show which amino acid was mutated in NHE1 or NHE2 to the amino acid present in the isoform shown at the tip of the arrow.

Na<sup>+</sup>/H<sup>+</sup> exchange isoforms which differ in amiloride sensitivity; and construction of point mutations in the various isoform Na<sup>+</sup>/H<sup>+</sup> exchangers to test the significance concerning amiloride sensitivity of several amino acids which are predicted as being important for amiloride binding [19, 84]. Franchi et al. [28, 29] used acid exposure in the presence of amiloride analogues as a selection criterion and succeeded in selecting two Chinese hamster lung fibroblast mutants, AR40 and AR300, that overexpressed a mutated Na<sup>+</sup>/H<sup>+</sup> exchanger. AR40 and AR300 were 10- and 30-fold less sensitive, respectively, to the 5'-amino substituted methylpropylamiloride (MPA) compared to the wild type (NHE1) control, but only 2-3.5-fold less sensitive to amiloride. Subsequent cloning and transfection of a cDNA coding the mutant exchanger from AR300 in PS120 cells expressed a Na<sup>+</sup>/H<sup>+</sup> exchanger with the same lower affinity to MPA that AR300 had compared to the wild type [19]. Identification of the mutation in AR40 and AR300 by complementation showed that the MPA resistance in both was conferred by a single basepair mutation at the codon for amino acid 167 (amino acid number refers to NHE1), which converted Leu to Phe (Table 2). The difference in AR40 and AR300 was related to gene amplification with more copies of the mutant gene expressed in AR300 and the fact that AR40 has co-existence of the mutated and wild type alleles [19]. Amino acid 167 is located in the fourth putative transmembrane helix.

The amino acid residues near Leu 167 are highly conserved among the Na<sup>+</sup>/H<sup>+</sup> exchanger isoform gene family (Fig. 4). To further understand the molecular basis of amiloride resistance among the known Na<sup>+</sup>/H<sup>+</sup> exchanger isoforms, both the Pouyssegur and Donowitz/Tse laboratories introduced mutational substitutions into either human NHE1 or rabbit NHE2, respectively, to mimic the other isoforms [19, 84] (Table 2). Using the amino acid numbering of NHE1, mutating Leu 167 to Phe increased the  $K_i$  for MPA/EIPA and amiloride, with a greater effect on sensitivity to MPA than to amiloride. Also Counillion and Pouyssegur showed that mutating Phe 165 to Tyr increased the  $K_i$  for MPA and amiloride, with a greater effect on sensitivity to amiloride than to MPA. The ability to affect the magnitude of the  $K_i$ s for amiloride or its 5'-amino substituted analogues suggests that the putative fourth transmembrane helix is likely to be part of the amiloride binding domain. In addition, based on differences in sensitivity to amiloride vs. MPA. amino acid Leu 167 likely interacts with the 5'-amino substituted part of amiloride, while the amino acid Tyr 165 probably interacts with a conserved part of amiloride, most likely the guanidinium group or the pyrazine ring [19, 84]. This suggests at least two attachment points for amiloride in the fourth membrane spanning domain. In addition, failure to reproduce amiloride  $K_i$  values of native  $Na^+/H^+$  exchangers by the mutational substitutions,

particularly in NHE2, suggests the presence of additional amiloride binding domains elsewhere or additional parts of the exchanger which affect amiloride binding. Of interest was the lack of change in  $K_m^{\rm Na^+}$  by the point mutations in NHE2 [84]. This suggested at least a second site of amiloride binding and/or that Na<sup>+</sup> and amiloride do not bind at the identical site, as initially suggested by Pouyssegur [28].

#### REGULATION

## (1) Short-Term Regulation

Protein kinases regulate the rate of Na<sup>+</sup>/H<sup>+</sup> exchange, although how that occurs is not yet understood at a molecular level. In native fibroblasts, Pouvssegur et al. demonstrated that the Na<sup>+</sup>/H<sup>+</sup> exchanger was stimulated by thrombin and EGF, with thrombin acting via phosphatidylinositol turnover, while EGF acted by affecting tyrosine phosphorylation [14, 44–46]. NHE1 is a phosphoprotein [67, 68] and the amount of phosphorylation on serine of the same specific phosphopeptide in NHE1 changes with exposure to EGF and thrombin in parallel with the change in intracellular pH, likely due to a change in Na<sup>+</sup>/H<sup>+</sup> exchange rate. Also the phosphatase 1 and 2A inhibitor okadaic acid, which would be expected to increase phosphorylation on the assumption that phosphorylation is present under basal conditions, increases phosphorylation of NHE1 and increases the basal intracellular pH. It also adds to the stimulatory effect of EGF and thrombin [67]. Nonetheless, it is unknown if changes in the phosphorylation of the Na<sup>+</sup>/H<sup>+</sup> exchanger or in an associated protein lead to changes in the Na<sup>+</sup>/H<sup>+</sup> exchange rate.

Phosphopeptide mapping demonstrated that NHE1 had changes in phosphorylation in response to both thrombin and EGF but that these changes occurred only on serine residues with no tyrosine phosphorylation identified [67]. This indicated that an intermediate kinase was involved in EGF regulation. This has been postulated to involve MAP kinase (mitogen activate protein kinase) [67]. In addition, it has been postulated that NHE1 may be more directly regulated by a kinase associated with the exchanger, perhaps similar to the regulation of the  $\beta$ -adrenergic receptor by a receptor-related kinase [68, 78].

Concerning mechanisms of regulation, it is hypothesized that the phosphorylated NHE C-terminus is coupled to the internal H<sup>+</sup> modifier site and that phosphorylation is crucial to allow interaction of the two parts of the exchanger, since depleting

intracellular ATP alters the H<sup>+</sup> modifier site functionally [46, 77].

There are multiple unanswered questions concerning regulation of Na<sup>+</sup>/H<sup>+</sup> exchange rate by phosphorylation including: while nearly all recognized putative protein kinase consensus sequences are in the C-terminal portion of the NHE, is it only the C-terminal portion that is phosphorylated? Are the epithelial isoform NHEs only phosphorylated on serine or are they also phosphorylated on tyrosine or threonine? Are the intermediates postulated as being involved in regulation of NHE1, which includes MAP kinase, also involved in regulation of the epithelial isoforms? Does location in the plasma membrane domain in an epithelial cell change the mechanism of regulation via phosphorylation? Is a specific serine residue responsible for regulation by a specific kinase or is there redundancy in the serines, as is suggested to occur for regulation of CFTR by cAMP [5]?

Not all functional changes in Na<sup>+</sup>/H<sup>+</sup> exchange rate appear to be carried out via phosphorylation. Specifically, NHE1 involvement in cell swelling following osmotic shrinkage is dependent on ATP, but is not associated with a change in the amount of phosphorylation of NHE1 [33]. Thus, Grinstein et al. proposed dual control mechanisms of NHE1 by phosphorylation-dependent and phosphorylation-independent mechanisms [33].

Regulation of the three stably expressed Na<sup>+</sup>/H<sup>+</sup> exchanger isoforms, NHE1, NHE2 and NHE3, by external signals and second messengers differs both in mechanism and in direction of regulation. It is thought that second messenger regulation of NHE1 is mediated through reversible phosphorylation-dependent coupling of the C-terminal cytoplasmic domain with the H<sup>+</sup> modifier site [67, 69, 78]. NHE1 activity is stimulated by growth factors, including, insulin, and also by thrombin and phorbol esters [46, 67, 69, 73] (Fig. 5). In the presence of these factors, the exchanger shows increased affinity for  $[H^+]_i$ , with no change in  $V_{\text{max}}$ . It has been hypothesized that this increased affinity occurs at the H<sup>+</sup> modifier site, thus enhancing the allosteric properties of the exchanger.

NHE2 activity is also stimulated by growth factors, thrombin and phorbol esters, but with different kinetic characteristics [46]. These agents induce an increase in  $V_{\rm max}$  with no apparent change in affinity for H<sup>+</sup> [46]. NHE3 exhibits yet another difference in regulation, with stimulation by growth factors, serum and thrombin, but with inhibition by phorbol esters [46, 73] (Fig. 5). This is similar to the C kinase regulation seen in the rabbit ileal villus cells and rat colonic brush border Na<sup>+</sup>/H<sup>+</sup> exchangers involved in electroneutral NaCl absorption [18, 20, 21], and

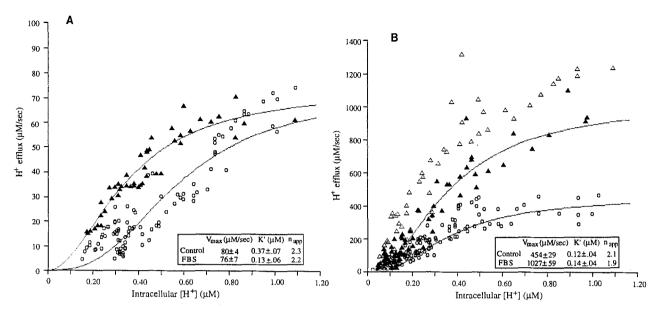


Fig. 5. Effect of serum on Na<sup>+</sup>/H<sup>+</sup> exchange rate of NHE1 and NHE3, stably expressed in PS120 fibroblasts. FBS stimulated Na<sup>+</sup>/H<sup>+</sup> exchange rate in PS120/NHE1 and NHE3 cells when added at the beginning of the Na<sup>+</sup>-dependent pH recovery. In this figure, control cells ( $\bigcirc$ ) were acidified with an NH<sub>4</sub>Cl prepulse and allowed to recover in Na<sup>+</sup> medium, while treated cells ( $\triangle$ ) were similarly acidified, then perfused with Na<sup>+</sup> medium containing 10% FBS. (A) For PS120/NHE1 cells, the stimulation in exchanger activity was not reflected in an elevated  $V_{\text{max}}$ , rather a decrease in K'H<sup>+</sup><sub>i</sub> was seen. In contrast, for PS120/NHE3 (B) cells, there was an increase in  $V_{\text{max}}$  with addition of FBS. When PS120/NHE3 cells ( $\triangle$ ) were incubated with the PKC inhibitor H7 (65  $\mu$ M) for 10 min prior to addition of Na<sup>+</sup> medium with 10% FBS, there was a greater stimulation of exchanger activity. Incubation with H7 alone did not change the exchanger activity compared with control cells (data not shown).

also to the C kinase response of the  $Na^+/H^+$  exchanger present on the apical surface of the OK proximal tubule cell line [35]. The effect of all these factors on the kinetics of NHE3 activity is similar to that seen with NHE2; a change in  $V_{\rm max}$  with no apparent change in affinity for  $H^+$ .

Studies of the effect of cAMP on the cloned Na<sup>+</sup>/H<sup>+</sup> exchangers are difficult to interpret, as variable results have been reported for the different isoforms when expressed in various cell types. Of note, there is no consensus sequence for cAMP in the cytoplasmic C-terminus of NHE1 suggesting indirect regulation, if it occurs [69]. In the OK cell line, the apical Na<sup>+</sup>/H<sup>+</sup> exchanger is inhibited by cAMP [35]. OK cells lack basolateral Na<sup>+</sup>/H<sup>+</sup> exchange and also lack NHE1 normally. However, when NHE1 is transfected into OK cells a basolateral Na+/H+ exchanger appears and it is inhibited by cAMP (H. Murer, J. Pouyssegur, unpublished observations). In a SV-40 transformed rabbit kidney proximal tubule cell line (RKPC-2), NHE2 appears to be present on the apical surface and NHE1 on the basolateral membrane, with both exchangers inhibited in the presence of cAMP [55]. In the PS120 transfected fibroblasts, there was no effect of cAMP on the activity of any of the exchangers [46], and in the Caco-2 cell line there is no effect of cAMP on

the activity of the endogenous NHE1 antiporter, which is present only on the basolateral membrane [79]. Only one antiporter expressed in PS120 cells ( $\beta$ -NHE1 cloned from trout red blood cells) is regulated cAMP; this exchanger is stimulated by cAMP, but only under conditions of high external pH (7.8) [7]. This isoform has two cAMP-dependent protein kinase consensus sequences in the cytoplasmic C-terminus which are separated by only four amino acids [6]. Thus, cAMP effects are widely variable, which is explained partially but not entirely by the putative protein kinase consensus sequences in the individual Na<sup>+</sup>/H<sup>+</sup> exchanger isoform C-terminus, and at least partially seems to be dependent on the cell type which contains the NHE.

C kinase is involved in regulation of NHEs. The amino acid composition of the NHE appears to determine the C kinase regulation. C kinase stimulates NHE1 and NHE2 and inhibits NHE3 all expressed in PS120 cells. C kinase increases Na<sup>+</sup>/H<sup>+</sup> exchange by NHE1 expressed in fibroblasts and in the basolateral membranes of the SV-40 transfected cell line of rabbit S2 proximal tubules (RKPT-2) as well as in that normally occurring in the proximal tubule cell line LLC-PK<sub>1</sub>. The only exception is Caco-2 cells in which C kinase has no effect on NHE1 in the basolateral membrane.

Another way to study the role of phosphorylation in regulation of Na<sup>+</sup>/H<sup>+</sup> exchange is via studying the effects of ATP depletion. ATP-depletion studies of NHE1 have shown that depleting ATP eliminates regulation of Na<sup>+</sup>/H<sup>+</sup> exchange rate by growth factors and protein kinases [77]. In addition, while the ATP-depleted exchanger maintains almost full activity at low pH and there is still evidence of a H<sup>+</sup> modifier site, the affinity for H<sup>+</sup> is reduced and the exchanger is inactivated at a lower pH than in ATP-replete cells [77]. Not all studies support that NHE1 is affected by ATP depletion with a decrease only in  $H^+$  affinity and not in  $V_{\text{max}}$ . In rat aortic smooth muscle, which is thought to contain NHE1, ATP depletion altered the affinity but also decreased the  $V_{\text{max}}$  [48]. It must be emphasized that it is not known if aortic smooth muscle contains other Na+/H+ exchanger isoforms. In ATP-depletion studies of NHE2 and NHE3, there are similar findings relating to the modifier site, with persistence of the modifier site and with a reduced H+ affinity; in addition, ATP depletion reduces  $V_{\text{max}}$  of the exchangers, even at high intracellular H+ concentrations (low pH) [46]. This implies that although in NHE2 and NHE3 the H<sup>+</sup> modifier site does not appear to be influenced by changes in second messengers above conditions of basal phosphorylation, the basal level of phosphorylation influences the internal modifier site function, as it does for NHE1. In addition, these studies show that the internal modifier site functions in the dephosphorylated exchanger and in the absence of ATP. Also consistent with the observations that regulation of NHE2 and NHE3 involves changes in  $V_{\text{max}}$  is the demonstration that reducing ATP lowers their  $V_{\text{max}}$ .

# (2) Long-Term Regulation—Effects of Glucocorticoids on Ileal Brush Border Na<sup>+</sup>/H<sup>+</sup> Exchange

It had been previously shown that glucocorticoids stimulate intestinal water and NaCl absorption [15], which in the rabbit takes approximately 18 hr to reach a maximum effect. Methylprednisolone stimulates rabbit ileal neutral NaCl absorption, whereas induction of glucocorticoid deficiency with aminoglutethimide inhibits NaCl absorption [70]. Studies were done to determine whether the mechanism of these longer term effects involved stimulation of ileal villus cell brush border Na<sup>+</sup>/H<sup>+</sup> exchange and if glucocorticoid regulation potentially involves a change in transcription of any NHE isoform [85]. Rabbits treated with methylprednisolone for 24 and 72 hr had increased ileal brush

border Na $^+/H^+$  exchange  $\sim 100\%$ , whereas aminogluthethimide treatment led to a 50% decrease in Na<sup>+</sup>/H<sup>+</sup> exchange (Fig. 6A). The effects on Na<sup>+</sup>/H<sup>+</sup> exchange were specific to the extent that diffusive Na+ uptake (no pH gradient), glucosedependent Na<sup>+</sup> uptake and Na<sup>+</sup> equilibrium volumes were not affected. Quantitation of message of NHE1, NHE2 and NHE3 showed that methylprednisolone stimulated NHE3 mRNA level by 4-6 fold (Fig. 6B). In contrast, messages for NHE1 and NHE2 were not affected by methylprednisolone. These results demonstrate that glucocorticoids regulate ileal Na+ uptake by an effect on the brush border Na<sup>+</sup>/H<sup>+</sup> exchanger. They are analogous to the earlier findings of Freiberg et al. [30] that the glucocorticoid dexamethasone, but not the mineralocorticoid aldosterone, increased rat proximal tubule brush border Na<sup>+</sup>/H<sup>+</sup> exchange, but had no effect on Na+-dependent glucose uptake or Na<sup>+</sup> uptake without a pH gradient. More importantly, this study suggests, although it does not prove, that NHE3 is the Na<sup>+</sup>/H<sup>+</sup> exchanger isoform involved in ileal NaCl absorption and in brush border Na<sup>+</sup>/H<sup>+</sup> exchange: that it is under basal control of glucocorticoids; and probably can be stimulated at the level of transcription by glucocorticoids (regulation by changes in mRNA stability is also possible).

Kinase/growth factor regulation of NHE2 and NHE3 is by changes in  $V_{\rm max}$ .  $V_{\rm max}$  changes have been postulated as being due to changes in turnover number of a transporter or in the number of active membrane proteins. Attempts were made to inhibit protein kinase regulation of NHE1, NHE2 and NHE3 expressed in PS120 fibroblasts with the microfilament inhibitor cytochalasin D; the microtubule inhibitor colchicine; and the golgi-golgi golgiendoplasmic reticulum vesicle trafficking inhibitor brefeldin A. None of these agents altered Na $^+/{\rm H}^+$  exchange.

The only hint of actin involvement in regulation of Na<sup>+</sup>/H<sup>+</sup> exchange has come from studies of serum regulation of basolateral Na+/H+ exchange (NHE1) in the polarized colon cancer cell line Caco-2 [80]. Removing serum reduces Na<sup>+</sup>/H<sup>+</sup> exchange rate, an effect which occurs in 2 hr, reaches a maximum in 4 hr and can be returned to full activity by adding serum back for 4 hr [80]. The removal and return of Na<sup>+</sup>/H<sup>+</sup> exchange is temperature dependent with both processes inhibited by reducing temperature to 13°C. The removal process but not the return process was inhibited by cytochalasin D, implicating actin in the process of lowering Na<sup>+</sup>/H<sup>+</sup> exchange following serum removal. Whether vesicle trafficking of NHE1 occurs is unknown.

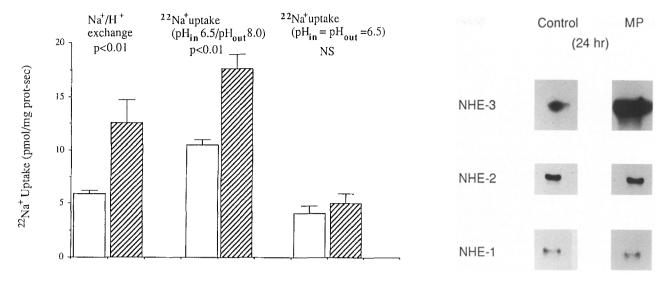


Fig. 6. (Left) Methylprednisolone increases ileal brush border Na<sup>+</sup>/H<sup>+</sup> exchange. Control animals were injected with saline and killed 24 hr later, whereas methylprednisolone-treated animals were injected once (40 mg daily) and also killed 24 hr later. Brush border vesicles were prepared from villus cells by magnesium precipitation. Initial rates of <sup>22</sup>Na<sup>+</sup> uptake were determined in the presence  $(pH_{in} 6.5/pH_{out} 8.0)$  (middle panel) or absence of an acid inside pH gradient ( $pH_{in} = pH_{out} = 6.5$ ) (right panel) and  $Na^+/H^+$  exchange was determined as the difference (left panel). Final Na+ concentration in the transport buffer was 1 mm. Both membrane and transport buffers contained 60 mm TMA/nitrate as a voltage clamp. Membrane buffer (15  $\mu$ l) and 30  $\mu$ l of transport buffer were mixed, and <sup>22</sup>Na<sup>+</sup> uptake was studied over 3, 5, and 8 sec at 25°C. Data represent slopes of the rate of uptake over time, and Na<sup>+</sup>/H<sup>+</sup> exchange rate was determined by subtracting Na+ uptake with a pH gradient minus Na+ uptake with no pH gradient at each time point and using those data to determine the rate of Na<sup>+</sup>/H<sup>+</sup> exchange in each experiment. Each data point represents the mean of quadruplicate determinations. Results are mean  $\pm$  se of the slopes representing Na<sup>+</sup> uptake from N separate experiments. P values are a comparison of slopes from paired individual experiments (paired t-tests). NS, not significant [reprinted from 85]. (

) Control; 

methylprednisolone, n = 3. (Right) Methylprednisolone treatment for 24 hr increases expression of Na<sup>+</sup>/H<sup>+</sup> exchanger message for NHE3 but not NHE2 or NHE1. A single representative experiment of ribonuclease protection assay of ileal villus cell RNAs from control and methylprednisolone-treated animals is shown. Total RNA was isolated, and ribonuclease protection assay was performed; 30 µg of total RNAs for NHE1 and NHE2 or 15 µg for NHE3 was loaded in each lane and separated on a 6% polyacrylamide gel [reprinted from 85].

## EFFECT OF CELL TYPE ON NHE PLASMA MEMBRANE LOCATION AND PROTEIN KINASE REGULATION

There is evidence that the cell type (epithelial or nonepithelial) can influence second messenger regulation of Na<sup>+</sup>/H<sup>+</sup> exchange, and that the different exchanger isoforms may be targeted to different membrane domains in polarized cells. Caco-2, a human intestinal epithelial cell line derived from a colon carcinoma, when grown in 10% serum normally expresses only NHE1, which is present only on the basolateral surface [79, 80]. Under these conditions, Caco-2 has no brush border Na<sup>+</sup>/H<sup>+</sup> exchanger, at least in the variant studied in our laboratory [79, 80]. Unlike in the PS120 fibroblasts, the Caco-2 cell endogenous NHE1 is not regulated acutely by serum, phorbol esters or growth factors [79]. However, the kinetic parameters for Na+ and H+ are similar for NHE1 in both PS120 cell and in Caco-2 cells, with evidence of an internal H<sup>+</sup> modifier site and Hill coefficient > 2 with respect to  $H^+$ . Thus,

cell type or location on a specific plasma membrane domain in a polarized epithelial cell influences protein kinase regulation of NHE1. Since NHE1 in the basolateral membrane of other epithelial cells is regulated by second messengers makes it less likely that it is the membrane location and more likely that it is cell type specific regulation which is involved.

When Caco-2 cells are transfected with NHE3 they express it predominantly, if not entirely, on the apical surface, suggesting that there is specific targeting to the brush border [47, 73]. NHE2 is also expressed on the Caco-2 apical surface, although it is not known if it also appears on the basolateral surface [47, 74]. In addition, second messenger regulation of NH3 in these transfected Caco-2 cells is similar to the regulation seen in transfected PS120 fibroblasts. PMA inhibits apical NHE3. This implies that these regulatory pathways are intact in the Caco-2 cells and that the lack of regulation of the endogenous NHE1 is due to a difference in the isoform subtype or to some cell specific aspect of Caco-2 cells.

#### References

- Ahearn, G.A., Franco, P. 1990. Sodium and calcium share the electrogenic 2Na<sup>+</sup>-1H<sup>+</sup> antiporter in crustacean antennal glands. Am. J. Physiol. 259:F758-F767
- Alpers, R.J. 1990. Cell mechanisms of proximal tubule acidification. *Physiol. Rev.* 70:79–114
- Aronson, P.S., Nee, J., Suhm, N.A. 1982. Modifer role of internal H<sup>+</sup> inactivating the Na<sup>+</sup>/H<sup>+</sup> exchange in renal microvillus membrane vesicles. *Nature* 299:161-163
- Benos, D.J. 1988. Amiloride: chemistry, kinetics, and structure-activity relationships. *In*: Na<sup>+</sup>/H<sup>+</sup> Exchange. S. Grinstein, editor. pp. 121-136. CRC, Boca Raton, FL
- Berger, H. A., Travis, S. M., Welsh, M. J. 1993. Regulation of the cystic fibrosis transmembrane conductance regulator Cl<sup>-</sup> channel by specific protein kinases and protein phosphatases. J. Biol. Chem. 268:2037-2047
- Biemesderfer, D., Reilly, R., Exner, M., Igarashi, P., Aronson, P. 1992. Immunocytochemical characterization of Na<sup>+</sup>/H<sup>+</sup> exchanger isoform NHE1 in rabbit kidney. *Am. J. Physiol.* 263:F833–F840
- Borgese, F., Sardet, C., Cappadoro, M., Pouyssegur, J., Motais, R. 1992. Cloning and expressing a cAMP-activated Na<sup>+</sup>/H<sup>+</sup> exchanger: evidence that the cytoplasmic domain mediates hormonal regulation. *Proc. Natl. Acad. Sci. USA* 89:6768-6769
- Boron, W.F. 1983. Transport of H<sup>+</sup> and ionic weak acids and bases. J. Membrane Biol. 72:1-16
- Brant, S.R., Bernstein, M., Wasmuth, J.J., Taylor, E.W., McPherson, J.D., Li, X., Walker, S.A., Pouyssegur, J., Donowitz, M., Tse, C.M., Jabs, E.W. 1993. Physical and genetic mapping of a human apical epithelial Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE-3) isoform to chromosome 5p15.3. Genomics 15:668-672
- Casavola, V., Guerra, L., Helmle-Kolb, C., Reshkin, S., Murer, H. 1992. Na<sup>+</sup>/H<sup>+</sup> exchange in A6 cells: polarity and vasopressin regulation. J. Membrane Biol. 130:105-114
- Casavola, V., Helmle-Kolb, C., Montrose, M.H., Murer, H. 1991. Polarized expression of Na<sup>+</sup>/H<sup>+</sup> exchange activities in clonal LLC-PK1 cells (Clone<sub>4</sub> and PKE<sub>20</sub>) cells. I. Basic characterization. *Pfluegers Arch.* 418:276–283
- Casavola, V., Helmle-Kolb, C., Murer, H. 1989. Separate regulatory control of apical and basolateral Na<sup>+</sup>/H<sup>+</sup> exchange in renal epithelial cells. *Biochem. Biophys. Res. Commun.* 165:833–837
- Casavola, V., Reshkin, S.J., Murer, H., Helmle-Kolb, C. 1992. Polarized expression of Na<sup>+</sup>/H<sup>+</sup> exchange activity in clonal LLC-PK1 cells (Clone<sub>4</sub> and PKE<sub>20</sub>) cells: Hormonal regulation. *Pfluegers Arch.* 420:282-289
- Chambard, J.C., Paris, S., L'Allemain, G., Pouyssegur, J. 1987. Two growth factor signaling pathways in fibroblasts distinguished by pertussis toxin. *Nature* 326:800-803
- Charney, A.N., Kinsey, M.D., Meyers, L., Giannella, R.A., Gots, R. 1978. Na-K activated adenosine triphosphatase and intestinal electrolyte transport—effect of adrenal steroids. J. Clin. Invest. 56:653-660
- Clark, J.D., Limbird, L.L. 1991. Na<sup>+</sup>/H<sup>+</sup> exchanger subtypes: a predictive review. Am. J. Physiol. 261:G945-G953
- Cohen, M.E., Reinlib, L., Gorelick, F., Rys-Sikora, K., Tse, M., Rood, R.P., Czernik, A.S., Sharp, C.W.G., Donowitz, M. 1990. Rabbit ileal villus cell brush border Na<sup>+</sup>/H<sup>+</sup> exchange is regulated by Ca<sup>2+</sup>/calmodulin dependent protein kinase II, a brush border membrane protein. *Proc. Natl. Acad. Sci. USA* 87:8990-8994
- 18. Cohen, M.E., Wesolek, J., McCullen, J., Pandol, S., Rood,

- R.P., Sharp, C.W.G., Donowitz, M. 1991. Carbachol and elevated Ca<sup>2+</sup>-induced translocation of functionally active protein kinase C to the brush border of ileal Na<sup>+</sup> absorbing cells. *J. Clin. Invest.* **88**:855–863
- Counillon, L., Franchi, A., Pouyssegur, J. 1993. A point mutation of the Na<sup>+</sup>/H<sup>+</sup> exchanger gene (NHE-1) and amplification of the mutated allele confer amiloride-resistance upon chronic acidosis. *Proc. Natl. Acad. Sci. USA* 90:4508-4512
- Donowitz, M., Cheng, H.Y., Sharp, G.W.G. 1986. Effects of phorbol esters on Na and Cl transport in rat colon. Am. J. Physiol. 251:509-517
- Donowitz, M., Cohen, M.E., Gould, M., Sharp, G.W.G. 1989. Elevated intracellular Ca<sup>2+</sup> acts through protein kinase C to regulate rabbit ileal NaCl absorption: Evidence for sequential control by Ca<sup>2+</sup>/calmodulin and protein kinase C. *J. Clin. Invest.* 83:1953–1962
- Donowitz, M., Welsh, M.J. 1987. Regulation of mammalian small intestinal electrolyte transport. *In*: Physiology of the Gastrointestinal Tract. L.R. Johnson, editor. pp. 1351-1388. Raven, New York
- Donowitz, M., Wicks, J., Madara, J.L., Sharp, G.W.G. 1985.
   Studies on the role of calmodulin in Ca<sup>2+</sup> regulation of rabbit ileal Na<sup>+</sup> and Cl<sup>-</sup> transport. Am. J. Physiol. 248:726-740
- Emmer, E., Rood, R.P., Wesokel, J.H., Cohen, M.E., Braithwaite, R.S., Sharp, G.W.G., Murer, H., Donowitz, M. 1989. The role of calcium and calmodulin in the regulation of the rabbit ileal brush border membrane Na<sup>+</sup>/H<sup>+</sup> antiporter. J. Membrane Biol. 108:207-215
- Engelman, D.M., Goldman, A., Steitz, T.A. 1982. The identification of helical segments in the polypeptide chain of Bacteriorhodopsin. *Methods Enzymol.* 88:81–89
- Fliegel, L., Haworth, R.S., Dyck, J.R.B. 1993. Characterization of the placental brush border membrane Na<sup>+</sup>/H<sup>+</sup> exchanger: Identification of thio-dependent transition in apparent molecular size. *Biochem. J.* 289:101–107
- Fliegel, L., Sardet, C., Pouyssegur, J., Barr, A. 1991. Identification of the protein and cDNA of the cardiac Na<sup>+</sup>/H<sup>+</sup> exchanger. FEBS Lett. 279:25-29
- Franchi, A., Cragoe, E., Pouyssegur, J. 1986. Isolation and properties of fibroblast mutants overexpressing an altered Na<sup>+</sup>/H<sup>+</sup> antiporter. J. Biol. Chem. 261:14614-14620
- Franchi, A., Perucca-Lostanten, D., Pouyssegur, J. 1986.
   Functional expression of a human Na<sup>+</sup>/H<sup>+</sup> antiporter gene transfected into antiporter-deficient mouse L cells. *Proc. Natl. Acad. Sci. USA* 83:9388-9392
- Freiberg, J.M., Kinsella, J., Sacktor, B. 1982. Glucocorticoids increase the Na<sup>+</sup>/H<sup>+</sup> exchange and decrease the Na<sup>+</sup> gradient-dependent phosphate-uptake systems in renal brush border membrane vesicles. *Proc. Natl. Acad. Sci. USA* 9:4932-4936
- Grinstein, S., Rotin, D., Marson, M.J. 1989. Na<sup>+</sup>/H<sup>+</sup> exchanger and growth factor-induced cytosolic pH change. Role in cellular proliferation. *Biochim. Biophys. Acta* 988:73-91
- Grinstein, S., Smith, I.D. 1987. Asymmetry of the Na<sup>+</sup>/H<sup>+</sup> antiport of dog red cell ghosts, sidedness of inhibition by amiloride. *J. Biol. Chem.* 262:9088-9092
- Grinstein, S., Woodside, M., Sardet, C., Pouyssegur, J., Rotin, D. 1992. Activation of the Na<sup>+</sup>/H<sup>+</sup> antiporter during cell volume regulation. Evidence for a phosphorylation-independent mechanism. J. Biol. Chem. 267:23823-23828
- Hanley, R.M., Shenolikar, S., Pollack, J., Steplock, D., Weinman, E.J. 1990. Identification of calcium/calmodulin multifunctional protein kinase II in rabbit kidney. *Kidney Int.* 38:63-66

- Helme-Kolb, C., Montrose, M.H., Murer, H. 1990. Parathyroid hormone regulation of Na<sup>+</sup>/H<sup>+</sup> exchange in opossum kidney cells. Polarity and mechanisms. *Pfluegers Arch.* 416:615–623
- Hildebrandt, F., Pizzona, J.H., Reilly, R.F., Rebouc, N.A., Sardet, C., Pouyssegur, J., Slayman, C.N., Aronson, P.S., Igarashi, P. 1991. Cloning of cDNA encoding a rabbit renal Na<sup>+</sup>/H<sup>+</sup> exchanger—tissue distribution and comparison to the human sequence. *Biochim. Biophys. Acta* 1129:105– 108
- 37. Jia, Z.P., McCullough, N., Martel, R., Hemmingsen, S.K., Young, P.G. 1992. Gene amplification at a locus encoding a putative Na<sup>+</sup>/H<sup>+</sup> antiporter confers sodium and lithium tolerance in fission yeast. *EMBO*. J. 11:1631–1640
- Karpel, R., Alon, T., Glaser, G., Schuldiner, S., Padan, E. 1991. Expression of sodium proton antiporter (NhaA) in Escherichia coli as induced by Na<sup>+</sup> and Li<sup>+</sup> ions. J. Biol. Chem. 265:20297-20302
- Knickelbein, R.G., Aronson, P.S., Dobbins, J.W. 1990. Characterization of Na<sup>+</sup>/H<sup>+</sup> exchangers on villus cells in rabbit ileum. Am. J. Physiol. 259:G802–G806
- Kopito, R., Lodish, H.F. 1985. Primary structure and transmembrane orientation of the murine anion exchange protein. *Nature* 316:234-238
- Krapf, R., Alpern, R.J. 1993. Cell pH and transepithelial H/HCO<sub>3</sub> transport in renal proximal tubule. J. Membrane Biol. 131:1-10
- Krapf, G., Solioz, M. 1991. Na<sup>+</sup>/H<sup>+</sup> antiporter in RNA expression in single nephron segments of rat kidney cortex. J. Clin. Invest. 88:783-788
- Kyte, J., Doolittle, R.F. 1992. A simple method for displaying the hydrophobic character of a protein. J. Mol. Biol. 157:103-132
- L'Allemain, G., Paris, S., Pouyssegur, J. 1984. Growth factors action and intracellular pH regulation in fibroblasts. Evidence for a major role of the Na<sup>+</sup>/H<sup>+</sup> antiporter. J. Biol. Chem. 259:5809-5815
- L'Allemain, G., Seuwen, K., Velu, T., Pouyssegur, J. 1989.
   Signal transduction in hamster fibroblasts overexpressing the human EGF receptor. *Growth Factors* 1:311-321
- Levine, S., Yun, C., Montrose, M., Tse, C.M., Donowitz, M. Detailed characterization of three cloned mammalian Na<sup>+</sup>/H<sup>+</sup> exchangers stably expressed in a fibroblast cell line. (in preparation)
- Levine, S., Yun, C., Montrose, M., Tse, C.M., Donowitz, M. 1993. Plasma membrane sorting and C kinase regulation of three cloned Na<sup>+</sup>/H<sup>+</sup> exchangers expressed in an epithelial cell line, Caco-2. *Gastroenterology* 104:259A
- Little, P.J., Weissberg, P.L., Cragoe, E.J., Bobik, A. 1988. Dependence of Na<sup>+</sup>/H<sup>+</sup> antiporter in cultured rat aortic smooth muscle on calmodulin, calcium, and ATP. Evidence for the involvement of calmodulin-dependent kinases. *J. Biol. Chem.* 263:16780–16786
- Marra, M.A., Prasad, S.S., Baillie, D.L. 1993. Molecular analysis of two genes between let-56 in the unc-22(IV) region of Caenorhabditis elegans. Mol. Gen. Genet. (in press).
- Mattei, M.G., Sardet, C., Franchi, A., Pouyssegur, J. 1988.
   The human amiloride-sensitive Na<sup>+</sup>/H<sup>+</sup> antiporters: localization to chromosome 1 by in situ hybridization. Cytogenet. Cell. Censt. 48:6–8
- Miller, R.T., Pollock, A.S. 1987. Modification of the internal pH sensitivity of the Na<sup>+</sup>/H<sup>+</sup> antiporter by parathyroid hormone in a cultured renal cell line. *J. Biol. Chem.* 262:9115-9210
- 52. Montrose, M.H., Murer, H. 1990. Polarity and kinetics of

- $Na^+/H^+$  exchange in cultured opossum kidney cells. *Am. J. Physiol.* **259**:C121–C133
- Morell, G., Steplock, D., Shenolikar, S., Weinman, E.J. 1990. Identification of a putative Na<sup>+</sup>/H<sup>+</sup> exchanger regulatory co-factor in rabbit renal BBM. Am. J. Physiol. 259:F867-F871
- Mrkic, B., Forgo, J., Murer, H., Helmle-Kolb, C. 1992. Apical and basolateral Na/H exchange in cultured murine proximal tubule cells (MCT): Effect of parathyroid hormone (PTH). J. Membrane Biol. 130:205-217
- Mrkic, B., Tse, C.M., Forgo, J., Helmle-Kolb, C., Donowitz, M., Murer, H. 1993. Identification of PTH-responsive Na<sup>+</sup>/H<sup>+</sup> exchanger—isoforms in a rabbit proximal tubule cell line (RKPC-2). *Pfluegers Arch. (in press)*
- Murer, H., Hopfer, U., Kinne, R. 1976. Sodium, proton antiport in brush border membranes isolated from rat small intestine and kidney. *Biochem. J.* 154:597-602
- Nicholl, D.A., Longoni, S., Philipson, K.D. 1990. Molecular cloning and functional expression of the cardiac sarcolemmal Na-Ca exchanger. *Science* 250:562–565
- Opleta-Madsen, K., Hardin, J., Gall, D.G. 1991. Epidermal growth factor up regulates intestinal electrolyte and nutrient transport. Am. J. Physiol. 260:G807-G814
- Orlowski, J., Kandasamy, R.A., Shull, G.E. 1992. Molecular cloning of putative members of the Na<sup>+</sup>/H<sup>+</sup> exchanger gene family. J. Biol. Chem. 267:9332–9339
- Pinner, E., Kotler, Y., Padan, E., Schuldiner, S. 1993. Physiological role of NhaB, specific Na<sup>+</sup>/H<sup>+</sup> antiporter Escherichia coli. J. Biol. Chem. 268:1729-1734
- 61. Pouyssegur, J., Sardet, C., Franchi, A., L'Allemain, G., Paris, S. 1984. A specific mutation abolishing Na<sup>+</sup>/H<sup>+</sup> antiport activity in hamster fibroblasts precludes growth at neutral and acidic pH. *Proc. Natl. Acad. Sci. USA* 81:4833–4837
- Rajendran, V.M., Binder, H.J. 1990. Characterization of Na<sup>+</sup>/H<sup>+</sup> exchanger in apical membrane vesicles of rat colon. J. Biol. Chem. 265:8408-8414
- Raley-Susman, K.M., Cragoe, E.J., Jr., Sapolsky, R.M., Kopito, R.R. 1991. Regulation of intracellular pH in cultured hippocampal neurons by an amiloride-insensitive Na<sup>+</sup>/H<sup>+</sup> exchanger. J. Biol. Chem. 266:2739-2745
- 64. Reidel, B.D., Kikuchi, K., Ghisan, F.K. 1989. Ileal brush border Na<sup>+</sup>/H<sup>+</sup> exchange: the effect of epidermal growth factor and mechanism of action. Gastroenterology 96:415A
- 65. Reilly, R.F., Hildebrandt, F., Biemesderfer, D., Sardet, C., Pouyssegur, J., Aronson, P.S., Slayman, C.N., Igarashi, P. 1991. cDNA cloning and immunolocalization of a Na<sup>+</sup>/H<sup>+</sup> exchange in LLC-PK<sub>1</sub> renal epithelial cells. *Am. J. Physiol.* 261:F1088-F1094
- 66. Reuss, L., Petersen, K.U. 1985. Cyclic AMP inhibits Na<sup>+</sup>/H<sup>+</sup> exchange at the apical membrane of *Necturus* gallbladder epithelium. J. Gen. Physiol. 85:409-429
- Sardet, C., Counillon, L., Franchi, A., Pouyssegur, J. 1990.
   Growth factors induce phosphorylation of the Na<sup>+</sup>/H<sup>+</sup> antiporter, a glycoprotein of 110 kD. Science 247:723-726
- 68. Sardet, C., Fafournox, P., Pouyssegur, J. 1991. Thrombin epidermal growth factor, and okadaic acid activate the Na<sup>+</sup>/H<sup>+</sup> exchanger, NHE1, by phosphorylating a set of common sites. J. Biol. Chem. 266:19166-19171
- Sardet, C., Franchi, A., Pouyssegur, J. 1989. Molecular cloning, primary structure and expression of the human growth factor—activatable Na<sup>+</sup>/H<sup>+</sup> antiporter. Cell 56:271-280
- Sellin, J.H., Field, M. 1981. Physiologic and pharmacologic effects of glucocorticoids on ion transport across rabbit ileal mucosa in vitro. J. Clin. Invest. 67:770-778

- Takaichi, K., Wang, D., Blakovets, D.F., Warnock, D.G. 1992. Cloning, sequencing, and expression of Na<sup>+</sup>/H<sup>+</sup> antiporter cDNAs from human tissues. Am. J. Physiol. 262:C1069-C1076
- Tse, C.M., Brant, S.R., Walker, S., Pouyssegur, J., Donowitz, M. 1992. Cloning and sequencing a rabbit cDNA encoding an intestinal and kidney-specific Na<sup>+</sup>/H<sup>+</sup> exchanger isoform (NHE-3). *J. Biol. Chem.* 267:9340–9346
- 73. Tse, C.M., Levine, S.A., Yun, C.H., Brant, S.R., Pouyssegur, J., Montrose, M.H., Donowitz, M. 1993. Functional characteristics of a cloned epithelial Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE3): resistance to amiloride and inhibition of protein kinase C. Proc. Natl. Acad. Sci. USA (in press)
- Tse, C.M., Levine, S.A., Yun, C.H.C., Montrose, M.H., Little, P.J., Pouyssegur, J., Donowitz, M. 1993. Cloning and expression of a rabbit cDNA encoding a serum-activated ethylisopropyl amiloride resistant epithelial Na<sup>+</sup>/H<sup>+</sup> exchanger isoform (NHE-2). J. Biol. Chem. 268: 11917-11924
- Tse, C.M., Ma, A.I., Yang, V.W., Watson, A.J.M., Potter, J., Sardet, C., Pouyssegur, J., Donowitz, M. 1991. Molecular cloning of cDNA encoding the rabbit ileal villus cell basolateral membrane Na<sup>+</sup>/H<sup>+</sup> exchanger. *EMBO*. J. 10:1957– 1967
- Vigne, P., Frelin, C., Lazdunski, M. 1985. The Na<sup>+</sup>/H<sup>+</sup> antiporter is activated by serum and phorbol ester in proliferating myoblasts but not in differentiated myotubes. Properties of the activation process. J. Biol. Chem. 260:8008-8013
- Wakabayashi, S., Fafournoux, P., Sardet, C., Pouyssegur, J. 1992. The Na<sup>+</sup>/H<sup>+</sup> antiporter cytoplasmic domain mediates growth factor signals and controls H<sup>+</sup> sensing. *Proc. Natl.* Acad. Sci. USA 89:2424–2428
- Wakabayashi, S., Sardet, C., Fafournoux, P., Counillon, L., Meloche, S., Pages, G., Pouyssegur, J. 1992. Structure

- function of the growth factor-activatable Na<sup>+</sup>/H<sup>+</sup> exchange (NHE-1). Rev. Physiol. Biochem. Pharmacol. **119:**157–186
- Watson, A.J.M., Levine, S., Donowitz, M., Montrose, M.H. 1991. Kinetics and regulation of polarized Na<sup>+</sup>/H<sup>+</sup> exchanger from Caco-2 cells, a human intestinal cell line. *Am. J. Physiol.* 261:G229–G238
- Watson, A.J.M., Levine, S., Donowitz, M., Montrose, M.H. 1992. Serum regulates Na<sup>+</sup>/H<sup>+</sup> exchange in Caco-2 cells by a mechanism which is dependent on F-actin. *J. Biol. Chem.* 267:956-962
- Weinman, E.J., Dubinsky, W.P., Dinh, Q., Steplock, D., Shenolikar, S. 1989. Effect of limited trypsin digestion on the renal Na<sup>+</sup>/H<sup>+</sup> exchanger and its regulation by cAMPdependent protein kinase. *J. Membrane Biol.* 109:233-241
- 82. Weinman, E.J., Dubinsky, W., Shenolikar, S. 1989. Regulation of the renal Na<sup>+</sup>/H<sup>+</sup> exchanger by protein phosphorylation. *Kidney Int.* 36:519-525
- Weinman, E.J., Steplock, D., Bui, G., Yuan, N., Shenolikar,
   S. 1990. Regulation of renal Na<sup>+</sup>/H<sup>+</sup> exchanger by cAMP-dependent protein kinase. Am. J. Physiol. 258:F1254–F1258
- 84. Yun, C.H.C., Little, P.J., Tse, C.M., Pouyssegur, J., Donowitz, M. 1993. Amino acid 143 in membrane spanning domain 4 determines the sensitivity to amiloride in a cloned epithelial Na<sup>+</sup>/H<sup>+</sup> exchanger, NHE-2. Biochem. Biophys. Res. Comm. (in press)
- 85. Yun, C.H., Gurubhagavatula, S., Levine, S.A., Montgomery, J.M., Brant, S.R., Cohen, M.E., Pouyssegur, J., Tse, C.M., Donowitz, M. 1993. Glucocorticoid stimulation of ileal Na<sup>+</sup> absorptive cell brush border Na<sup>+</sup>/H<sup>+</sup> exchange and association with an increase in message for NHE-3, an epithelial isoform Na<sup>+</sup>/H<sup>+</sup> exchanger. J. Biol. Chem. 268:206–211
- 86. Yusufi, A.N.K., Szczeparska-Konkel, M., Dousa, T.P. 1988. Role of N-linked oligosaccharides in the transport activity of the Na<sup>+</sup>/H<sup>+</sup> antiporter in rat renal brush border membrane. J. Biol. Chem. 263:13683–13691