manica females attain similar peak rates of JH biosynthesis as do the CA of intact females[16, 17] (fig. 1) and they become significantly hypertrophied, but here too, the total number of CA cells remains constant. These results clearly argue against changes in the total number of CA cells having a significant role in the regulation of JH biosynthesis in *B. germanica*. Furthermore, they suggest that the ovaries do not regulate the total number of CA cells in the adult cockroach.

Sexual dimorphism in JH synthesis by the CA is common in insects[19], but it is not clear when and how this divergence occurs. In adult *D. punctata*, the CA of males have fewer cells and a lower capacity for JH synthesis than female CA[20]. In *B. germanica*, these intrinsic differences appear to arise during CA development late in the last nymphal instar when developmental patterns of male and female nymphs diverge. During nymphal development the increase in CA volume and proliferation of CA cells are thought to be associated mainly with somatic growth[19]. However, in female *B. germanica* the number of CA cells increases most rapidly late in the last instar while the greatest gain in body mass occurs earlier in the instar. The female-specific increases in CA volume and cell number are therefore only partly related to somatic growth in the nymph, and appear to be independent of JH biosynthesis by the CA.

We conclude that, in *B. germanica*, the activity of the CA is independent of changes in its total number of cells. It is unlikely that CA cell proliferation plays a major role in regulating JH biosynthesis in either the last instar or the adult, since at both stages the changes in activity are not associated with changes in cell number. However, a significant female-specific cell proliferation in the last instar may be a prerequisite for the higher activity of the CA in the adult female than in the adult male.

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Cyclic and linear vasopressin V_1 and V_1/V_2 antagonists containing arginine in the 4-position

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Summary. Substitution of arginine for glutamine in the 4-position of a vasopressin V_1 antagonist has been reported to turn it into an agonist. We resynthesized this 4-arginine analog and synthesized additional cyclic and linear vasopressin antagonists containing a 4-arginine. The presence of a 4-arginine in the resynthesized and new analogs had relatively minor effects on their antivasopressin V_1 and V_2 antagonistic potencies.
Key words. Vasopressin antagonists; V_1-antagonists; V_2-antagonists; neurohypophysial hormones; arginine.

Several amino acids occupy the 4-position in vertebrate neurohypophysial hormones. All known tetrapod neurohypophysial hormones contain 4-glutamine in this position while neurohypophysial peptides containing 4-serine or 4-asparagine also appear among fishes. 4-Arginine has been suggested as a hypothetical evolutionary intermediate that might explain how peptides containing 4-glutamine, 4-serine and 4-asparagine could have been derived

from each other during vertebrate phylogeny[1]. This interesting possibility gains support from the recent finding that 4-arginine analogs of arginine-vasotocin, the 'conopressins', do indeed occur in the venoms of certain fish-eating snails of the genus *Conus*[2].

Rekowski et al.[3] reported that the substitution of a 4-arginine in arginine-vasopressin resulted in rather modest reductions in antidiuretic and vasopressor activities, by about 1/2 and 1/4, respectively. The same substitution in the potent V_1 antagonist, $d(CH_2)_5$AVP ([1-(β-mercapto-β,β-cyclopentamethylenepropionic acid)] arginine-vasopressin), however, resulted in what appeared to be a dramatic reversal of its pharmacological properties. The 4-arginine analog of this vasopressin V_1 antagonist became an effective V_1 agonist[3].

The recent identification of natural peptides among invertebrates that resemble arginine-vasotocin but contain 4-arginine[2], and the report that 4-arginine substitution could turn an antagonist into an agonist[3], prompted us to examine the effects of this substitution in a number of neurohypophysial hormone analogs. The pharmacological properties of the conopressins and some related 4-arginine-containing agonistic analogs of vasotocin are reported elsewhere[4]. In this note we wish to report our findings on the effects of substituting 4-arginine in vasopressin V_1 and V_1/V_2 antagonists.

Materials and methods

The protected precursors required for the synthesis of the free peptides 1 through 9 (tables 1 and 2) were synthesized by the solid-phase method (I, II and VI through IX, table 3) or by a combination of solid-phase and solution methods, by 8 + 1 coupling (compounds III through V) according to previously described procedures[5-9]. Na in liquid NH_3 was used for deprotection[10,11] and the free peptides were purified by gel filtration on Sephadex G-15[12]. The homogeneity of all free peptides was checked by TLC, HPLC and amino-acid analysis. The physicochemical properties of the protected (compounds I through IX) and the free peptides (compounds 1 through 9) are presented in tables 3 and 4, respectively.

Peptides were assayed for biological activities by methods that have been described elsewhere in more detail[13]. Antidiuretic agonistic and antagonistic (V_2) activities were estimated by intravenous injection into hydrated rats under ethanol anesthesia[14]. Anti-vasopressor (V_1) activity was estimated by intravenous injection into rats under urethane anesthesia pretreated with phenoxybenzamine[15]. The USP posterior pituitary reference standard was used as a standard in the agonistic assays and as an agonist in the assays for antagonistic activities. In assays for antagonism the intravenous dose of an antagonist that would reduce the response to the subsequent

Table 1. Substitution of 4-arginine for 4-glutamine in potent and specific cyclic and linear vasopressin V_1 antagonists

Peptide[a]	ADH Activity (U/mg) (U/mg)	Anti-vasopressor ED (nmole/kg)
A. $d(CH_2)_5$AVP[b]	0.03	0.56 ± 0.11
B. $d(CH_2)_5$[Arg^4]AVP[c]	1.5	(agonist, 28 U/mg)
C. $d(CH_2)_5$[Arg^4]AVP[d]		0.50 ± 0.09
1. $d(CH_2)_5$[Arg^4]AVP[e]	0.13	0.54 ± 0.14
D. $d(CH_2)_5$[Tyr(Me)^2]AVP[b]	0.31	0.16 ± 0.01
2. $d(CH_2)_5$[Tyr(Me)^{2}Arg^4]AVP[e]	mixed[f]	0.24 ± 0.03
E. $d(CH_2)_5$[Tyr(Me)^{2}Ala-NH$_2$^{9}]AVP[g]	mixed[f]	0.12 ± 0.02
3. $d(CH_2)_5$[Tyr(Me)^{2}Arg^4-Ala-NH$_2$^{9}]AVP[e]	(ED = 3.1 ± 0.4)	0.22 ± 0.03
4. $d(CH_2)_5$[Tyr(Me)^{2}Val-NH$_2$^{9}]AVP[e]	mixed[f]	0.20 ± 0.04
5. $d(CH_2)_5$[Tyr(Me)^{2}Arg^4-Val-NH$_2$^{9}]AVP[e]	mixed[f]	0.20 ± 0.04
6. Aaa-D-Tyr(Et)-Phe-Gln-Asn-Abu-Pro-Arg-Arg-NH$_2$[e]	(ED = 16 ± 2)	0.48 ± 0.08
7. Aaa-D-Tyr(Et)-Phe-Arg-Asn-Abu-Pro-Arg-Arg-NH$_2$[e]	(ED = 1.9 ± 0.2	1.3 ± 0.1

[a] Abbreviations: AVP = arginine-vasopressin; $d(CH_2)_5$ = 1-β-mercapto-β,β-cyclopentamethylenepropionic acid; Tyr(Me) = O-methyltyrosine, Abu = alpha-aminobutyric acid; D-Tyr(Et) = (O-ethyl)-D-tyrosine; Aaa = 1-adamantaneacetyl. [b] Kruszynski et al.[16]. [c] Assay values reported by Rekowski et al.[3]. [d] Our assays on a sample of the peptide reported by Rekowski et al.[3] and kindly provided by B. Lammek. [e] This paper. [f] These analogs showed weak agonistic and antagonistic activities on these assays. [g] Manning and Sawyer[17].

Table 2. Substitution of 4-arginine for 4-valine in potent and nonspecific cyclic and linear vasopressin V_1/V_2 antagonists

Peptide[a]	Anti-antidiuretic (V_2) ED (nmole/kg)	Anti-vasopressor (V_1) ED (nmole/kg)	Potency ratio: V_2/V_1
F. $d(CH_2)_5$[D-Tyr(Et)^{2}Val^4]AVP[b]	1.1 ± 0.2	0.45 ± 0.11	0.41
8. $d(CH_2)_5$[D-Tyr(Et)^{2}Arg^4]AVP[c]	1.4 ± 0.1	0.30 ± 0.06	0.21
G. $d(CH_2)_5$[D-Ile^{2}Val^4]AVP[d]	0.70 ± 0.08	8.2 ± 1.4	12
9. $d(CH_2)_5$[D-Ile^{2}Arg^4]AVP[e]	0.70 ± 0.05	1.4 ± 0.2	2.0
H. Aaa-D-Tyr(Et)-Phe-Val-Asn-Abu-Pro-Arg-Arg-NH$_2$[e]	0.53 ± 0.07	1.2 ± 0.2	2.3
7. Aaa-D-Tyr(Et)-Phe-Arg-Asn-Abu-Pro-Arg-Arg-NH$_2$[e]	1.9 ± 0.2	1.3 ± 0.1	0.68

[a] See footnote (a) to table 1. [b] Manning et al.[18]. [c] This paper. [d] Manning et al.[19]. [e] Manning et al.[20].

Table 3. Physicochemical properties of the protected peptides (I to IX)

No.	Protected peptide[a]	Molecular formula	Yield[b] (%)	m.p. (°C)	$[\alpha]_D^{25}$, deg. (c = 1, DMF)	TLC B (R_f)[c] A	B	C	D
I	$d(CH_2)_5$[Arg^4]AVP	$C_{87}H_{108}N_{16}O_{15}S_4$	87	118–120	−32.1	0.61		0.71	0.80
II	$d(CH_2)_5$[Tyr(Me)^{2}Arg^4]AVP	$C_{81}H_{104}N_{16}O_{15}S_4$	85	126–129	−31.7	0.56		0.72	0.90 (9:3)
III	$d(CH_2)_5$[Tyr(Me)^{2}Arg^{4}Ala-NH_2^{9}]AVP	$C_{82}H_{106}N_{16}O_{15}S_4$	63	190–193	−29.7	0.74	0.79	0.74	0.86
IV	$d(CH_2)_5$[Tyr(Me)^{2}Val-NH_2^9]AVP	$C_{76}H_{100}N_{14}O_{14}S_3$	83	232–233	−36.3	0.71	0.72	0.79	0.82
V	$d(CH_2)_5$[Tyr(Me)^{2}Arg^{4}Val-NH_2^{9}]AVP	$C_{84}H_{110}N_{16}O_{15}S_4$	22	177–178	−31.7	0.78	0.80	0.82	0.86
VI	Aaa-D-Tyr(Et)-Phe-Gln-Asn-Abu-Pro-Arg-Arg-NH_2	$C_{76}H_{105}N_{17}O_{16}S_2$	79	158–160	−22.4	0.42		0.69	0.68
VII	Aaa-D-Tyr(Et)-Phe-Arg-Asn-Abu-Pro-Arg-Arg-NH_2	$C_{84}H_{115}N_{19}O_{17}S_3$	75	158–161	−17.1	0.54		0.70	0.87
VIII	$d(CH_2)_5$[D-Tyr(Et)^{2}Arg^4]AVP	$C_{82}H_{106}N_{16}O_{15}S_4$	94	139–146	−15.2	0.65	0.69	0.82	
IX	$d(CH_2)_5$[D-Ile^{2}Arg^4]AVP	$C_{77}H_{104}N_{16}O_{14}S_4$	65	143–148	−23.2	0.64	0.60	0.80	

[a] The structures of the protected precursors are as follows: $d(CH_2)_5$(Bzl)-Tyr(Bzl)-Phe-Arg(Tos)-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2, (I); $d(CH_2)_5$(Bzl)-Tyr(Me)-Phe-Arg(Tos)-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2, (II); $d(CH_2)_5$(Bzl)-Tyr(Me)-Phe-Arg(Tos)-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2, (III); $d(CH_2)_5$(Bzl)-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Val-NH_2, (IV); $d(CH_2)_5$(Bzl)-Tyr(Me)-Phe-Arg(Tos)-Asn-Cys(Bzl)-Pro-Arg(Tos)-Val-NH_2, (V); Aaa-D-Tyr(Et)-Phe-Gln-Asn-Abu-Pro-Arg(Tos)-Arg(Tos)-NH_2, (VI); Aaa-D-Tyr(Et)-Phe-Arg(Tos)-Asn-Abu-Pro-Arg(Tos)-NH_2, (VII); $d(CH_2)_5$(Bzl)-D-Tyr(Et)-Phe-Arg(Tos)-Asn-Cys(Bzl)-Pro-Arg(Tos)-GlyNH_2, (VIII); $d(CH_2)_5$(Bzl)-D-Ile-Phe-Arg(Tos)-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2, (IX). [b] Yields were calculated on the basis of glycine, alanine, valine or arginine content of the starting resin. [c] TLC systems: A, butan-1-ol-acetic acid-water (4:1:1, v/v/v); B, butan-1-ol-acetic acid-water (4:1:5, v/v/v); C, butan-1-ol-acetic acid-water-pyridine (15:3:3:10, v/v/v/v); D, chloroform-methanol (7:3), v/v).

Table 4. Physicochemical properties of the free peptides (1 to 9)

No. Peptide	Yield[a,b] (%)	$[\alpha]_D^{25}$, deg. (c = 0.1, 50%C AcOH)	TLC[c] B (R_f) A	B	C	E
1. $d(CH_2)_5$[Arg^4]AVP	82	−44(c = 0.3)	0.13	0.14	0.25	
2. $d(CH_2)_5$[Tyr(Me)^{2}Arg^4]AVP	71	−44(c = 0.3)	0.07	0.07	0.26	
3. $d(CH_2)_5$[Tyr(Me)^{2}Arg^{4}Ala-NH_2^{9}]AVP	53	−50	0.20	0.07		0.42
4. $d(CH_2)_5$[Tyr(Me)^{2}Val-NH_2^{9}]AVP	55	−65	0.23	0.18		
5. $d(CH_2)_5$[Tyr(Me)^{2}Arg^{4}Val-NH_2^{9}]AVP	38	−57	0.15	0.30	0.30	
6. Aaa-D-Tyr(Et)-Phe-Gln-Asn-Abu-Pro-Arg-Arg-NH_2	61	−47(c = 0.3)	0.10	0.12	0.37	
7. Aaa-D-Tyr(Et)-Phe-Arg-Asn-Abu-Pro-Arg-Arg-NH_2	93	−55	0.07	0.08	0.29	
8. $d(CH_2)_5$[D-Tyr(Et)^{2}Arg^4]AVP	34	−80		0.27	0.25	0.58
9. $d(CH_2)_5$[D-Ile^{2}Arg^4]AVP	65	−84	0.08	0.22	0.28	

[a] Yields are based on the amount of protected peptides used in the reduction-reoxidation step in each case. [b] All the free peptides gave the expected amino acid analysis ratios after hydrolysis ± 3%. [c] TLC, A, B and C are as in table 3. E is butan-1-ol-acetic acid-water (2:1:1, v/v/v). HPLC analyses showed 96 to 99% purity of all free peptides shown above.

injection of one unit of agonist to the level of the response to 1/2 unit in the absence to the antagonist was considered the 'effective dose', indicated in the tables as the 'ED'. Means ± SE's presented in the tables represent results of at least four independent assays.

Results and discussion

4-Arginine substitutions in vasopressin V_1 antagonists. When we examined the pharmacological properties of our resynthesis of $d(CH_2)_5$[Arg^4]AVP (peptide 1, table 1) we found that its V_1-antagonistic potency was essentially the same as that of its parent (peptide A). This was in marked contrast to the report by Rekowski et al.[3] that their synthesis of this analog (peptide B, table 1) resulted in a peptide with substantial agonistic activity. We therefore obtained a sample from their synthesis (peptide C, table 1) and found that its V_1-antagonistic activity was the same as that of our product (peptide 1) and that of the 4-glutamine-containing parent compound (peptide A) by our assays.

We also prepared 4-arginine analogs of three other potent cyclic V_1 antagonists (peptides D, E and 4). The 4-arginine derivatives (peptides 2, 3 and 5) appeared to retain most of the V_1-antagonistic potencies of their parent 4-glutamine analogs. However, when 4-arginine was substituted for 4-glutamine in a linear V_1 antagonist (peptide 6) the V_1-antagonistic potency of its 4-arginine analog (peptide 7) was reduced by about 2/3.

Our findings that the substitution of 4-arginine in four potent cyclic vasopressin V_1 antagonists caused little or no reduction in V_1-antagonistic potencies appear to stand in marked contrast to the reversal of antagonistic potency in one of these reported by Rekowski et al.[3]. Since our assays appear to show that the Rekowski et al. 4-arginine analog (peptide C) exhibits the same V_1-antagonistic potency as did our preparation of the same peptide we cannot explain the reason for this discrepancy. It is unlikely that differing assay conditions could explain these puzzling results since both Rekowski et al.[3] and we used the same vasopressor assay method[15].

4-Arginine substitutions in V_1/V_2 antagonists. Substitution of 4-arginine for 4-valine in two cyclic V_1/V_2 antagonists (peptides F and G, table 2) did not significantly affect V_2-antagonistic potencies. V_1-antagonistic potency was unchanged in one 4-arginine derivative (peptide 8)

and actually increased about sixfold in the other (peptide 9). Thus, although the parent peptide (peptide G) was a rather selective V_2 antagonist, with a V_2/V_1 potency ratio of about 12, the 4-arginine-substituted analog (peptide 9) was much less specific, with a V_2/V_1 potency ratio of about 2.

When a 4-arginine was substituted in a potent linear V_1/V_2 antagonist (peptide H) this reduced V_2-antagonistic potency by about 3/4 while V_1-antagonistic potency remained unchanged (peptide 7). When one compares the properties of peptides 6, 7 and H (tables 1 and 2), which contain 4-glutamine, 4-arginine and 4-valine, respectively, it appears clear that the 4-valine moiety favored V_2-antagonistic potency while the 4-glutamine favored V_1-antagonistic potency. The 4-arginine analog (peptide 7) had intermediate properties, being about equally potent as a V_1 and V_2 antagonist.

These findings suggest that, from a limited number of comparisons, the substitution of 4-arginine for 4-glutamine or 4-valine in V_1 and V_1/V_2 antagonists is generally well-tolerated. Most antagonistic potencies are either preserved or somewhat decreased with no clear gains in antagonistic specificities. In general, it seems remarkable that substitution of arginine, an amino acid with a highly basic and hydrophilic side chain for amino acids with more neutral and hydrophobic side chains, glutamine or valine, has such relatively minor effects on agonistic[3,4] or antagonistic activities of these vasopressin analogs.

Since the peptides containing 4-arginine would be more highly charged than their 4-glutamine or 4-valine counterparts their distribution would be expected to be more limited by cellular membranes and the blood-brain barrier. Such highly charged peptides could be useful in those experimental circumstances in which one wishes to try to limit their distribution, to restrict their actions to the brain after intracerebral injection, for example. By exerting more localized actions they could become more incisive pharmacological tools.

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Adrenal corticosteroidogenesis after removal of ventral prostate gland

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Summary. Removal of the ventral prostate gland in adult male rats causes an increase in adrenal weight, and stimulation of adrenal Δ^5-3β-hydroxysteroid dehydrogenase activity along with elevation of serum levels of corticosterone and prolactin.
Key words. Prostatectomy; adrenal Δ^5-3β-HSD; serum corticosterone; serum prolactin.