ciated from the cluster. This leads to a criterion for the stabilization of a cognitive process (cf. ref. 1) according to which:

$$\frac{(k_c + m_c)!}{k_c!\, m_c!} > \frac{(k_d + m_d)!}{k_d!\, m_d!} \qquad (13)$$

where the index c represents elements which belong to or are added to the cluster, and the index d represents elements that are involved in dissociation of an element m. This expression implies that the stability of a cognitive process of full complexity increases if there are more copies of an added interacting element than of a subtracted element. In other words, common interacting elements are favored at the expense of less common interacting elements if there is competition between them. During this process, the composite element is qualitatively changed.

As for the association parameter, it is obvious that it should somehow reflect the composition and stability of a weighted cognitive plasma as given in eq. (1) in four-dimensional space, where time is one dimension. The contained elements are defined by the sub-elements having the highest flux densities, ϱ, and, for each element k, in addition at least one or an arbitrary number of other sub-elements. For each element k and each value of ϱ_k, there is a group of other elements with lower values of ϱ which are contained in k and which can be called upon and included in the expression for cognitive stability at any time. This increases the associative power of the expression of cognitive stability in eq. (1) more than the mere repetition of the same higher element k. Therefore, just mentioning an abstraction does not have as much informative value as if it can be exemplified at the same time. On the other hand, it is obvious that elements with a sufficiently high level of abstraction must be chosen in order to exclude information that is not relevant. By doing so, it is possible to define any element precisely by measuring previous occurrences of a few sub-elements which are comparatively specific (in terms of a high value of ϱ) and the contexts in which the element has occurred. While the sub-elements can be observed in the spatial neighborhood of the element, the contextual elements can be observed in the temporal neighborhood Δt, as defined in eq. (7). Δt is related to the reduced complexity q, which means that human attention can be concentrated only on a few elements at a time and irrelevant information is forgotten. This is particularly evident in the 'anatomic learning phase' of higher organisms like man during the first months after birth, and the imprinting of a codified pattern of the environment. Only on the basis of such a 'hardware' – ground pattern can further perceptions be handled without danger of confusion[2]. Subsequently, the accumulated experience becomes increasingly important since it adds weight to the occurrence of individual elements and contexts in the actual situation.

The probability of a certain interaction from one element k to another element l is consequently given by the expressions eq. (9) and eq. (12) in which the association parameter A is the inverse of the maximal cognitive stability of the elements which have occurred within a time Δt framing the previous interactions between k and l:

$$A = \frac{1}{S_{max}} \qquad (14)$$

Some of these elements have already occurred in the particular context at time t, while others may frame the interaction in the immediate future. Therefore, the association parameter changes continuously as the specificity of the context is increased. With only a few elements specified the decay of the probability of an interaction between k and l at a given rate of the cognitive process $q/\Delta t$, may be so fast that the interaction does not occur. However, as other contexts are specified or anticipated by interactions involving other fundamental elements, the association parameter may become small enough to make probable an interaction between k and l.

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Short Communications

Responses of monkey, rabbit and dog internal carotid arteries to atrial natriuretic factor

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Summary. Effects of atrial natriuretic factor (ANF) on monkey, rabbit and dog internal carotid arteries were investigated. ANF caused a concentration-dependent relaxation in arterial strips submaximally precontracted with noradrenaline, 5-hydroxytryptamine, or high-potassium solution (10–30 mM). The response was greatest in the monkey arteries and least in the dog arteries. These results suggest that there is a marked species difference in the ANF-induced relaxation of the internal carotid arteries.
Key words. Atrial natriuretic factor (ANF); internal carotid artery; vasodilation.

Mammalian atria contain a potent natriuretic substance[1,2], which could be a novel peptide hormone of considerable importance for renal and cardiovascular homeostasis. This atrial natriuretic factor (ANF) also causes relaxation of isolated vascular and nonvascular smooth muscle preparations[3,4]. No detailed reports, however, have been made of the effects of ANF on cerebral arteries, except that by Faison et al.[5], who demonstrated a slight ANF-induced vasodilation in rabbit basilar artery. The

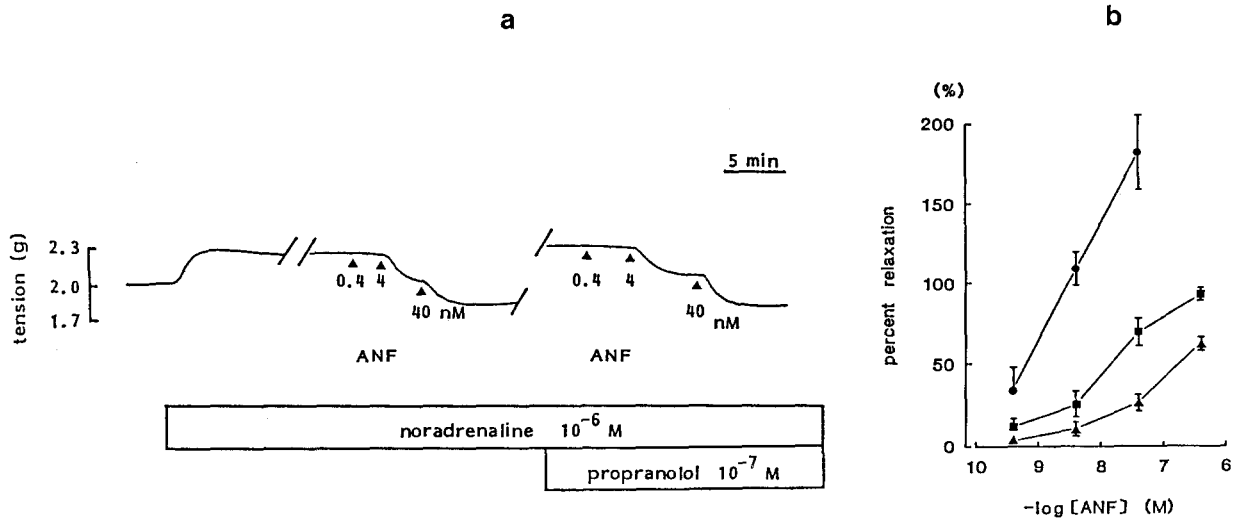

Figure 1. *a* A typical recording of the ANF-induced relaxation in isolated monkey internal carotid arterial strip precontracted with 10^{-6} M noradrenaline. Propranolol (10^{-7} M) was added to the normal Krebs solution 30 min before recurrent addition of ANF in the same strip. *b* Cumulative dose-response curves of isolated monkey (●), rabbit (■), and dog (▲) arterial strips to ANF. The abscissa shows the concentration of ANF in molarity on a log scale, and the ordinate denotes the degree of the ANF-induced relaxation expressed as a percentage of the submaximal contraction developed by 10^{-6} M noradrenaline (100% = 540 ± 120 mg in monkey, 120 ± 20 mg in rabbit, and 510 ± 140 mg in dog).

present study was undertaken to investigate effects of ANF on isolated monkey, rabbit and dog internal carotid arteries to shed light on the species difference in the ANF-induced cerebral vasodilation.

Materials and methods. Internal carotid arteries (ICA) were removed from anesthetized macaque monkeys (2.6–3.5 kg), white rabbits (4.2–4.3 kg) and mongrel dogs (10–18 kg), and cut into helical strips (1.0–1.5 × 15 mm). Each vascular strip was mounted in a 10-ml organ bath and perfused at a rate of 4 ml min^{-1} with Krebs solution aerated with 95% O_2 and 5% CO_2 (pH 7.4, 37 °C). The composition of the solution was as follows: [mM] NaCl 120.0, KCl 5.9, $NaHCO_3$ 25.0, NaH_2PO_4 1.2, $CaCl_2$ 2.5, $MgCl_2$ 1.2, and glucose 5.5. A tension of 1500–2000 mg was applied to each monkey and dog ICA strip and 900–1100 mg to each rabbit strip. The tension detected by an isometric transducer (Shinko UL-10) was recorded on a direct-writing oscillograph (Sanei 8K20). After a 90-min equilibration period, the strips were submaximally contracted by perfusion with the Krebs solution containing 10^{-6} M dl-noradrenaline hydrochloride (Sankyo), 3×10^{-8}–2×10^{-7} M 5-hydroxytryptamine (Sigma), or 10–30 mM KCl. Cumulative dose-response curves to ANF (synthesized α-rat atrial natriuretic polypeptide, amino acid 1–28, Bachem. Ltd., Peptide Institute Inc.) were then obtained in the absence or presence of 10^{-7} M propranolol hydrochloride (Sumitomo Kagaku). At the end of the experiments, sodium nitroprusside (Merck) ranging from 10^{-8} M to 10^{-4} M was applied to attain the maximum relaxation. Drug doses were expressed as final organ bath concentrations. Student's t-test was used to evaluate the significance, $p < 0.05$ being considered statistically significant.

Results and discussion. Figure 1a demonstrates typical responses of a monkey arterial strip to ANF. ANF caused a relaxation of the noradrenaline-induced contraction in a dose-dependent manner. Tachyphylaxis was not observed. The relaxant response to ANF was not affected by the pretreatment with 10^{-7} M propranolol. Cumulative dose-response curves of the arterial strips of monkey (n = 8), rabbit (n = 8), and dog (n = 9) are shown in figure 1b. The threshold concentrations of the relaxant response were less than 4×10^{-10} M for monkey and rabbit, and between 4×10^{-10} and 4×10^{-9} M for dog. Relaxation induced by ANF was greatest in monkey strips, medium in rabbit strips, and least in dog strips. In order to judge the importance of the relative sensitivities of monkey, rabbit and dog vessels to ANF, nitroprusside, a standard vasodilator, was administered at the end of each experiment to attain the maximum relaxation which was to be compared with the ANF-induced relaxation. Nitroprusside caused a dose-dependent relaxation in all internal carotid arteries, and the maximum responses were obtained with 10^{-6} M nitroprusside in monkey and dog arteries, and with 10^{-4} M in rabbit. The ratio of the 4×10^{-8} M ANF-induced relaxations to the maximum relaxations produced by nitroprusside was greatest in monkey (82.0 ± 4.2%, n = 7) and least (18.1 ± 5.5%, n = 7) in dog. Pretreatment with 5-hydroxytryptamine (3×10^{-8}–2×10^{-7} M) or high-potassium solution (10–30 mM) produced almost the same contractions of the monkey, rabbit and dog internal carotid arteries as those produced by noradrenaline 10^{-6} M, respectively. Administration of ANF also caused marked relaxations in the internal carotid arteries precontracted by 5-hydroxytryptamine and high potassium solution. The relative sensitivities of monkey, rabbit and dog carotid arteries to ANF were independent of the vasoconstrictive agents used; the decreasing order of sensitivity was monkey > rabbit > dog (fig. 2).

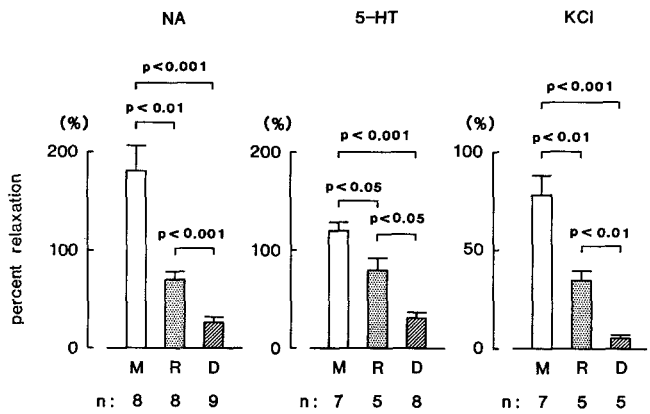

Figure 2. Effects of ANF (4×10^{-8} M) on the monkey (M), rabbit (R), and dog (D) arterial preparations precontracted by 10^{-6} M noradrenaline (NA), 3×10^{-8}–2×10^{-7} M 5-hydroxytryptamine (5-HT), or 10–30 mM KCl. The ordinate shows the degree of the ANF-induced relaxation expressed as percent of submaximal contraction developed by each vasoconstrictive agent. n, number of experiments.

The present results can be summarized as follows. 1) ANF produced a dose-dependent relaxation of isolated monkey, rabbit and dog internal carotid arteries. 2) The relaxations were not affected by the pretreatment with 10^{-7} M propranolol. 3) There was a marked species difference in the ANF-induced relaxation. The response was greatest in the monkey arteries and least in the dog arteries. 4) The relative sensitivities to ANF, which were represented as the ratios of the 4×10^{-8} M ANF-induced relaxations to the maximum relaxations developed by sodium nitroprusside, suggested the same tendency: greatest in monkey and least in dog.

The ANF is a peptide hormone which has a potent vasodilator activity as well as a natriuretic action[6]. Effects of ANF on rat and rabbit aorta, mesenteric and renal arteries are well studied[3,4]. Garcia et al.[4] suggested that there was a marked heterogeneity in the response of different vascular preparations to ANF.

Fujioka et al.[7] showed that i.v. infusion of 3 µg/kg ANF caused a significant fall in mean arterial pressure with no change in cerebral blood flow in anesthetized rat, implicating a fall in blood flow resistance in the brain. No report, however, has been found about the direct effect of ANF on isolated cerebral arteries except that by Faison et al.[5], who demonstrated a slight ANF-induced vasodilation in rabbit basilar artery.

Responsiveness of cerebral arteries to vasoactive substances is extremely different from that of extracranial arteries; 5-hydroxytryptamine is a more potent vasoconstrictor agent than noradrenaline in the cerebral arteries[8]. Responses of internal carotid artery to vasoactive agents are similar to those of cerebral arteries[9,10]. Thus, our results suggest that ANF may have a potent relaxant action on the monkey cerebral arterial smooth muscles. There is a marked species differences in the ANF-induced relaxation of the cerebral arteries. A low concentration (4×10^{-9} M) of ANF relaxed the monkey internal carotid arteries by almost 100%, the relative relaxation being expressed as percent of submaximal contraction developed by 10^{-6} M noradrenaline; and a higher concentration (4×10^{-8} M) of ANF produced further relaxation in those preparations. In contrast to the monkey strips, an ANF concentration a hundred times higher, 4×10^{-7} M, was needed to produce near 100% relaxation in rabbit arteries. Furthermore, the same concentration of ANF caused less relaxation (62.5 ± 3.6%) in the dog internal carotid arteries. Our results also show that the ANF-induced relaxation is not mediated by a beta-adrenergic receptors. This is consistent with the results obtained in the rat and rabbit strips[4]. Further study will be needed to clarify the mechanism of the ANF-induced relaxation.

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Na, K ATPase activity during early postnatal development of the rat submandibular gland

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Summary. The activity of the ouabain-sensitive Na, K ATPase was measured in membrane fractions of the submandibular gland of 1-, 7-, 14- and 21-day-old rats. This activity increased with age and reached adult levels by 21 days.
Key words. Submandibular gland; Na, K ATPase; postnatal development.

Slices of the rat submandibular gland exposed in vitro to appropriate secretagogues show a net release of K^+ which is the result of passive K^+ efflux balanced by K^+ reuptake[1,2]. The latter is inhibited by ouabain, which suggests that it occurs primarily by activation of a Na, K ATPase. Previous studies indicated that this ouabain-sensitive K^+ uptake was high in submandibular slices of newborn (i.e., 1-day-old) rats and became smaller as the age of the animals increased[3,4]. This finding suggested that the activity of the Na, K ATPase responsible for K^+ uptake changes as the gland matures during postnatal development. However, this K^+ uptake was measured in those studies under conditions which would markedly enhance pump activity, such as after a previous incubation in K^+-free medium, which results in K^+ loss and in Na^+ entry, i.e., in the type of change in cell electrolytes which would activate the Na, K pump. It was also observed that slices of 1-day-old rats also had a larger preceding passive efflux of K^+ under the experimental conditions used and that, at other ages, K^+ reuptake was also proportional to the preceding efflux. Thus, it was not clear if the differences in K^+ uptake observed at different postnatal ages were due to a change in the activity of the Na, K ATPase or to artifacts arising from the experimental conditions employed. The purpose of this study was, therefore, to directly measure Na, K ATPase at different postnatal ages, by using membrane fractions of the submandibular gland of 1-, 7-, 14- and 21-day-old rats. The results were compared with those obtained in fully mature glands of adult rats.

Methods. Pregnant Sprague Dawley rats were obtained from Sasco Laboratories approximately 1 week prior to delivery. The pups were maintained with the mothers and were removed when they reached the ages indicated above. They were anesthetized with i.p. injections of sodium pentobarbital and the submandibular glands were excised, minced on ice and homogenized at 4°C in 10 times (v/w) the volume of a buffer containing 25 mM imidazole, 300 mM sucrose, 1 mM phenylmethylsulfonyl fluoride (PMSF) and 2 mM dithiothreitol (DTT) in a Polytron homogenizer. An aliquot of the homogenate was removed for DNA analysis. The rest of the homogenate was centrifuged at $1000 \times g$ for 10 min and the resulting supernatant was then centrifuged at $100{,}000 \times g$ for 30 min. The resulting pellet was resuspended in 25 mM imidazole to a final concentration of 1–3