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RAPID COMMUNICATION

Bed Nucleus of the Stria Terminalis: Site for the Antinatriorexic Action of Tachykinins in the Rat

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POMPEI, P., S. J. TAYEBATY, G. DE CARO, J. SCHULKIN AND M. MASSI. *Bed nucleus of the stria terminalis: Site for the antinatriorexic action of tachykinins in the rat.* PHARMACOL BIOCHEM BEHAV **40**(4) 977–981, 1991.—The present study investigated the sensitivity of the posterior part of the medial division of the bed nucleus of the stria terminalis (BNST) to the antinatriorexic action of the tachykinin eledoisin in the rat. Salt appetite was evoked by sodium depletion following furosemide-induced natriuresis. The results obtained show that bilateral injection of eledoisin into the BNST evokes a very potent antinatriorexic effect, a statistically significant inhibition being observed even at the dose of 3.1 ng/BNST. On the other hand, when eledoisin was injected into the lateral ventricle, just above the BNST, much larger doses were required to elicit comparable inhibition of salt appetite. The antinatriorexic effect of eledoisin into the BNST is apparently behaviorally selective, since the same doses, which inhibited salt appetite, did not significantly affect the intake of 10% sucrose solution in the sodium-depleted animal. Present results suggest that the BNST is a site of action for the effect of tachykinins on salt appetite.

Tachykinins Eledoisin Salt appetite Bed nucleus of the stria terminalis

TACHYKININS (TKs) are biologically active peptides sharing the common carboxyterminal sequence PHE-X-GLY-LEU-MET·NH_2 (11). Several TKs have been found in the mammalian central nervous system: substance P (SP), neurokinin B (NKB), neurokinin A (NKA), NKA (3–10), neuropeptide K (NPK) and neuropeptide γ (NPγ) and show regional differences in their distribution (1, 16, 30, 39). At least 3 distinct TK receptor subtypes have been proposed for these peptides: the NK-1 (which preferentially interacts with SP), the NK-2 (which prefers NKA, NPK, and NPγ) and the NK-3 (which interacts best with NKB) (2, 4, 18, 20, 33, 34). A large body of evidence indicates the presence of NK-1 and NK-3 receptors in the central nervous system, while the presence of NK-2 receptors is still debated (18).

Previous studies indicate that TKs potently affect the behavioral regulation of body fluid in the rat. Intracerebroventricular (ICV) injections of TKs inhibit water intake induced by several dipsogenic treatments (6, 7, 8, 27, 32), as well as salt intake elicited by several natriorexigenic treatments (23, 24, 28, 29). Their effects on water and salt intake appear to be mediated by different receptor subtypes, which might account for the different spectrum of antidipsogenic and antinatriorexigenic actions of different TKs (26).

Little is known about where the TKs are acting in the brain. A recent study of our group showed that the medial region of the amygdala is a site of action for their inhibitory action on salt appetite (25). To gather more information on the neuroanatomical circuitry subserving the antinatriorexigenic action of TKs, we thought it interesting to evaluate the sensitivity of the dorsomedial part of the bed nucleus of the stria terminalis (BNST) to the inhibitory effect of TKs on salt appetite. Several reasons focused our attention on this nucleus: 1) the posterior part of the medial division of the BNST receives input from the medial amygdala, through afferent connections travelling in the stria terminalis (9,41); 2) as well as the medial amygdala, the BNST is rich in SP-containing perikarya, and is endowed with NK-1 and NK-3 receptors (5, 10, 19, 35, 38, 43); 3) finally, the BNST is involved in a number of sexually differentiated brain functions (13,40), it shows sex differences in the dimension of cell groups (3,17) and, in addition, it shows a dramatic sex difference in the pattern of SP-like immunoreactivity (21). Also, salt appetite is a sexually dimorphic behavior (14,36), thus raising the question of a possible linkage between sexual dimorphism for TKs in this nucleus and sex differences in regulation of salt intake.

The present study addressed the issue of the sensitivity of the BNST to the inhibitory action of the TK eledoisin (ELE) on sodium depletion-induced salt appetite in the male rat. ELE was the TK employed in the present study, since this is one of the most potent TKs of natural origin in inhibiting salt appetite in the rat (26).

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METHOD

Animals

Thirty adult male albino rats of the Sprague-Dawley strain (Holtzman, 425–475 g at the beginning of the experiments) were used. Animals were individually housed in a temperature-controlled room on a 12:12 light-dark cycle. Food in pellets (Diet No. 4RF18, Mucedola, Settimo Milanese, Italy) and water (in graduated drinking tubes) were available ad lib, except when noted. Rats had free access to sodium chloride (NaCl) solution (2%), except when required by the experimental procedure (see below).

Drugs

ELE (Peninsula Laboratories Europe, Merseyside, U.K.) and furosemide (Lasix; Hoechst Italia Sud, L'Aquila, Italy) were used.

Intracranial Surgery

All the rats employed were anaesthetized (Equithesin, 3 ml/kg b.wt.; intraperitoneally, IP) and fitted by stereotaxic surgery with two stainless steel guide cannulae bilaterally directed at the posterior part of the medial division of the BNST. The following coordinates were employed: AP = 1.3 mm behind the bregma, L = 1.3 mm from the sagittal suture, V = 5.5 mm from the dura, the surface of the skull being in a horizontal position. The AP coordinate corresponded to the anatomical situation reported at 0.8 mm behind the bregma in the atlas of Paxinos and Watson (31); the correction was required by the larger body weight of our animals.

The tip of the cannula was aimed only at 5.5 mm from the dura, to open into the lateral ventricle above the BNST. This allowed us to inject either into the lateral ventricle (with an injector as long as the cannula) or into the BNST (with an injector 2 mm longer than the cannula). Cannulae were attached to the skull by stainless steel screws and dental acrylic cement. Animals were allowed one week to recover from surgery before testing began.

Intracranial Injections

All the drugs employed were dissolved in sterile isotonic saline and injected by means of a stainless steel injector (o.d. 300 μ) temporarily inserted into the guide cannula. The small volume injected (0.2 μl into each BNST and 1 μl into each lateral ventricle) was administered with the aid of a 10-μl Hamilton microsyringe.

Experimental Procedures

Experiment 1: Effect of ELE injected into the BNST on sodium depletion-induced salt appetite. Salt appetite was elicited by an adaptation of the method of Wolf (42), in which depletion is produced by combining pharmacological natriuresis with sodium-deficient diet. Natriuresis was produced by subcutaneous (SC) injection of furosemide (2 injections of 5 mg/rat, separated by 2 h). At the time of the first injection, the pellets were replaced by sodium-deficient pellets (Code No. TD81263, Teklad, Madison, WI), 2% NaCl was removed from the cages, and cages were washed to remove adherent salt. The animals were not deprived of tap water. Twenty-two to 24 h later, they were injected into both BNST either with ELE or with isotonic saline (controls) and immediately afterwards, 2% NaCl was returned to them. Consumption of 2% NaCl and water, as well as latency to drink each solution, was recorded at 15, 30, 60, 90 and 120 min. Each animal received not more than 3 different treatments into the BNST at intervals of 7 days. Testing began with the third depletion, since the first depletions produce a lower intake of salt than the subsequent ones (37).

Experiment 2: Effect of ELE injected into the lateral ventricle on sodium depletion-induced salt appetite. Animals were sodium depleted as in Experiment 1. ELE or isotonic saline (controls) were bilaterally injected into the lateral ventricles, just before access to 2% NaCl. Each animal received 2 different treatments into the lateral ventricles at interval of 7 days.

Experiment 3: Effect of ELE injected into the BNST on 10% sucrose intake in sodium-depleted rats. This experiment was carried out to evaluate the behavioral selectivity of the antinatriorexigenic action of ELE injected into the BNST. The same animals tested in the previous experiments were employed. They were offered 10% sucrose solution 2 h a day for 7 days before the experiment began. Rats were then sodium depleted as in Experiment 1. Twenty-two h later, they were injected into both BNST with either isotonic saline, or with one of the 2 doses of ELE tested (12.5 or 50 ng/BNST). Immediately afterwards, they were returned to their home cages, where 10% sucrose was offered, instead of 2% NaCl. The intake of sucrose solution was recorded for 2 h.

Validation of ICV Injections

Validation of ICV injections was made by testing the animals with a dose of 50 ng/ventricle of angiotensin II. Only animals that drank at least 8 ml of water in 15 min after injection were included in the experimental group.

Histological Analysis

Upon completion of testing, rats were sacrificed with an overdose of anaesthetic, and brains were dissected free and kept in 10% formalin for at least a week. Histology was performed to evaluate the placement of the intracranial cannulae. Frozen brain sections (50 μ) were cut and stained with hematoxylin.

Statistical Analysis

Data are presented as means ± S.E.M. Statistical analysis of data was performed by multifactorial analysis of variance to check the overall significance. Planned pairwise comparisons were made by means of *t*-tests. Statistical significance was set at $p<0.05$.

RESULTS

Histological Analysis

Figure 1 shows all the valid placements of injector tips into the BNST, according to the Paxinos and Watson atlas (31). Successful bilateral placements into the BNST were obtained in about 70% of the implanted animals.

Eighteen rats showed valid injector tip placements at AP coordinates of −0.8 or −0.92 mm from the bregma, as reported in the atlas.

In two rats, the injector tips had a posterior localization (AP = −1.3), thus involving only the posterolateral part of the medial division of the BNST. The sensitivity of these two animals to the antinatriorexigenic action of ELE was not different

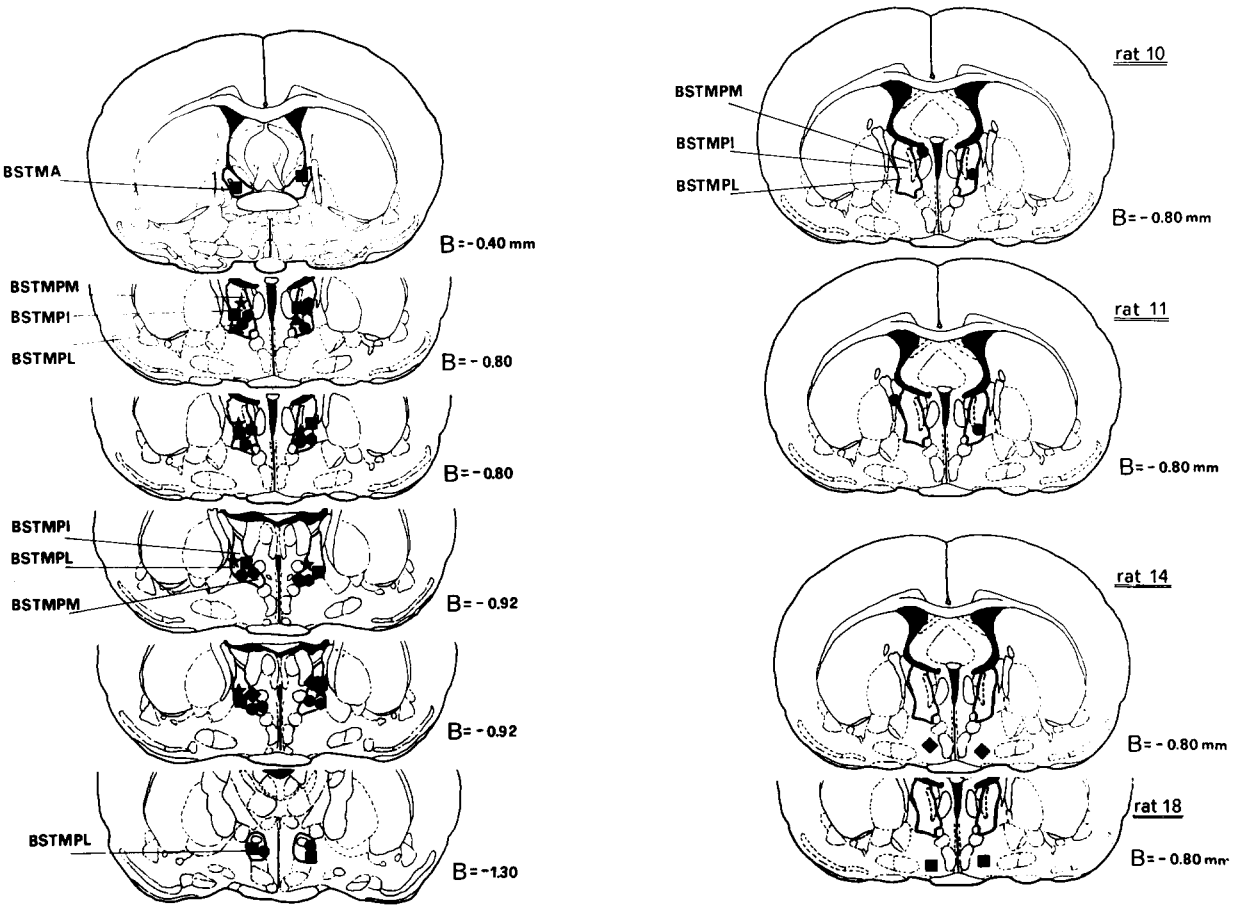

FIG. 1. The left panel shows bilaterally the end of the injector track into the BNST for all the rats with valid injector tip placements. The right panel shows examples of unsuccessful injector tip location. Different brain sections are identified by the antero-posterior coordinate (μ), taken from Paxinos and Watson atlas (31). Abbreviations (according to the atlas): BSTMA = bed nucleus of the stria terminalis, medial division, anterior; BSTMPM = bed nucleus of the stria terminalis, medial division, posteromedial; BSTPMI = bed nucleus of the stria terminalis, medial division, posterointermediate; BSTMPL = bed nucleus of the stria terminalis, medial division, posterolateral.

from that of the previous 18 rats.

In one rat, the injector tips were located at about −0.40 mm from the bregma. According to the atlas, the injector reached the most caudal region of the anterior part of the medial division of the BNST. Probably, injections of ELE in this animal may have influenced also the rostral region of the posterior part of the BNST. The sensitivity of this animal to ELE was similar to that of the previous rats, and the results obtained in it were pooled with those of the others.

The right panel of Fig. 1 shows two unilateral injector placements (rats #10 and #11). These rats proved to be less sensitive to the injections of ELE, and their data were discarded.

In two rats (rat #14 and #18), the injector tips proved to be 2 mm more ventrally than they were aimed at, owing to erroneous cannula placement. The injector tips ended into the medial preoptic area at the AP coordinate = −0.8 mm. These animals showed an even larger sensitivity to the antinatriorexigenic action of ELE. However, data from these animals were not used.

Of the remaining 5 rats, 3 died before completion of the experiments, while two had wrong ventral location of the cannula tips. In these animals, injections were made into the lateral ventricle and only marginally into the BNST. They showed a rather low sensitivity to ELE.

Experiment 1: Effect of ELE injected into the BNST on sodium depletion-induced salt appetite. As shown in Fig. 2 (upper panel), ELE evoked a potent antinatriorexigenic effect following injection into the BNST. The analysis of variance revealed a significant treatment effect, $F(4,57) = 10.575$, $p<0.0001$, as well as a significant time effect, $F(4,228) = 50.513$, $p<0.0001$, but no significant treatment-time interaction. Planned pairwise comparisons showed that the effect of ELE was statistically significant even at the dose of 3.1 ng/BNST during the entire 2-h period of observation. At the doses of 50 or 100 ng/BNST salt, intake was almost completely suppressed, respectively, in the first 30 or 60 min after access to salt.

Experiment 2: Effect of ELE injected into the lateral ventricle on sodium depletion-induced salt appetite. As shown in Fig. 2 (lower panel), the same doses of ELE used in Experiment 1 produced much lower reductions of salt intake when injected into the lateral ventricles. The overall analysis of variance revealed a nonsignificant treatment effect, $F(3,39) = 2.598$, $p = 0.065$, in the absence of treatment-time interaction, $F(12,156) = 1.051$, $p>0.05$.

Experiment 3: Effect of ELE injected into the BNST on 10% sucrose intake in sodium-depleted rats. The results of this experiment are presented in Fig. 3. At the doses tested, 12.5 or 50

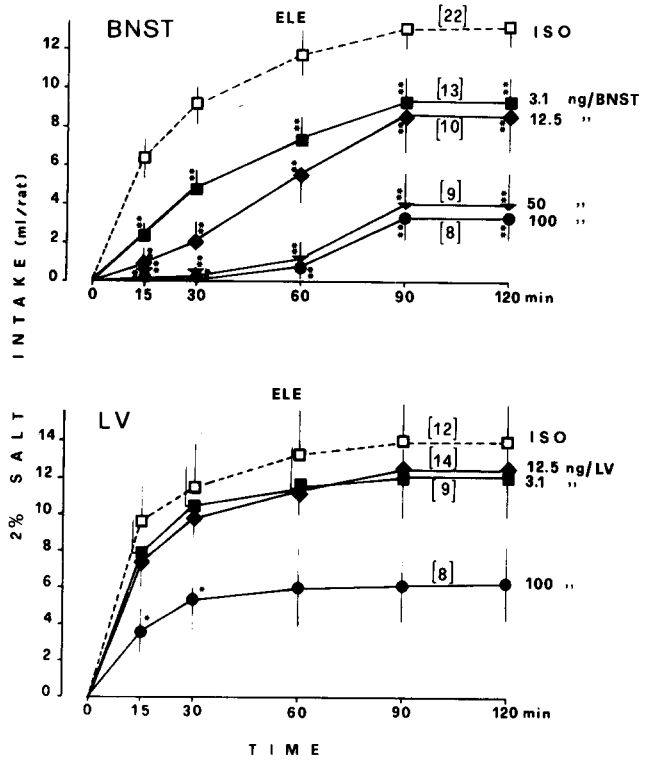

FIG. 2. Effect of bilateral injections (A) into the BNST or (B) into the lateral ventricles of different doses (ng/site) of ELE or of isotonic saline (ISO) on salt appetite induced by sodium depletion. Values are means ± S.E.M.; the number of subjects is given in parentheses. Statistical difference from controls (0): *$p<0.05$; **$p<0.01$; where not indicated, difference was not statistically significant.

ng/BNST, ELE did not significantly modify the intake of 10% sucrose solution in sodium-depleted rats, $F(2,27)=0.513$, $p>0.05$, in the absence of significant treatment-time interaction, $F(6,81)=1.157$, $p>0.05$.

DISCUSSION

The results of the present study show that injection of ELE into the BNST evokes a very potent inhibitory effect on sodium depletion-induced salt appetite in the rat.

The work of Johnson and Epstein (12) has shown that injections into the brain parenchyma with cannulae passing through the cerebral ventricles may result in backflow of the injectate into the ventricles. Once the injected substance has gained access to the cerebrospinal fluid, it can act at brain sites far from the injection site. In the present study, this problem was faced, first of all, by using a small volume of injection (0.2 μl) into the BNST, to reduce the possibility of diffusion. Moreover, direct injections of ELE into the lateral ventricles were made for control. ELE evoked a far more potent effect into the BNST than into the ventricle, thus indicating that: a) in our experimental conditions, diffusion into the ventricles is not sufficient for the

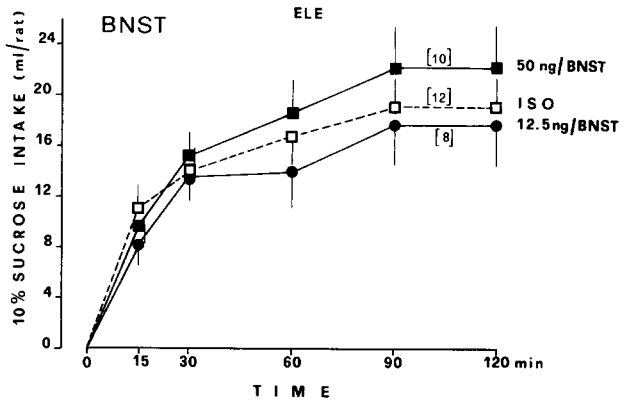

FIG. 3. Effect of bilateral injections into the BNST of different doses (ng/BNST) of ELE or of isotonic saline (ISO) on the intake of 10% sucrose solution. Values are means ± S.E.M.; the number of subjects is given in parentheses. Difference from controls, as in Fig. 2.

antinatriorexigenic effect observed following injection into the BNST and b) this nucleus per se should be responsible for the potent effect of ELE.

In addition, the results of Experiment 3 clearly show that the antinatriorexigenic effect of ELE into the BNST is behaviorally selective. In fact, the same doses that evoked a marked suppression of sodium depletion-induced salt appetite did not reduce the intake of 10% sucrose in the sodium-depleted rat. Moreover, other behaviors (such as grooming, scratching, locomotion, etc.) were not observed in our conditions.

Thus the results of the present study show that the BNST is a highly sensitive site of action for the inhibition of sodium depletion-induced salt appetite by ELE and suggest that the tachykininergic mechanisms in this nucleus might be selectively involved in the control of salt appetite.

Finally, a casual but interesting observation of this study is that also the medial preoptic area appears to be particularly sensitive to the antinatriorexigenic action of ELE. This finding is not surprising, since the BNST heavily projects to the medial preoptic area (9) and since this area is one of the most sensitive brain sites to the antidipsogenic action of TKs (22). However, further studies are needed to investigate in detail the sensitivity of the medial preoptic area to the antinatriorexigenic action of TKs.

A previous study of our group showed that the medial region of the amygdala, which heavily projects to the posterior part of the medial division of the BNST (9,41), is sensitive to the antinatriorexigenic action of TKs (25), even though less sensitive than the BNST. These findings suggest that the medial amygdala, the BNST and possibly the medial preoptic area might be components of the neuroanatomical circuitry subserving the antinatriorexigenic action of TKs.

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