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Neuropeptide K potently stimulates salivary gland secretion and potentiates substance P-induced salivation

(tachykinins/β-preprotachykinin/neurokinin A/submandibular ganglia/otic ganglia)

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ABSTRACT **Neuropeptide K (NPK) is an N-terminally extended derivative of neurokinin A (NKA) that can be a final product in the posttranslational processing of β-preprotachykinin. A rat salivation bioassay was used to demonstrate potent effects of NPK at low doses, while effects due to NKA were much weaker at higher doses. The rank order of potency of β-preprotachykinin-derived peptides on salivation responses was NPK > substance P > NKA ≫ β-preprotachykinin-(72–96)-peptide. The time course of the NPK response was longer than that observed with substance P. The responses elicited by NPK were blocked by the tachykinin antagonist [D-Pro^2, D-Trp^{7,9}]substance P but not by atropine. In peptide coinfusion studies, NPK strikingly potentiated the salivation responses elicited by substance P. NPK *in vitro* displayed a 100 times lower potency than substance P in displacing ^{3}H-labeled substance P binding in submandibular gland membranes, a tissue rich in SP-P type (NK-1) receptors. The possible cellular mechanisms by which NPK stimulates salivary gland secretion are discussed. We conclude that NPK and substance P may be cotransmitters derived by posttranslational processing of β-preprotachykinin.**

The tachykinin peptides are a family of structurally related neuropeptides that are under consideration as neurotransmitter or neuromodulatory substances. Mammalian peptides in this family include substance P (SP), neurokinin A (NKA), neuropeptide K (NPK), and neurokinin B (NKB; for review, see ref. 1). The former three peptides are derived from the SP gene (2, 3), whereas NKB is derived from a separate gene (2–4). In rats, the SP gene primary transcript is differentially spliced into three mRNAs called α-, β-, and γ-preprotachykinin (PPT). The β-PPT mRNA possesses the full complement of exons (2, 3) and can be translated (5) and processed posttranslationally to yield SP and NKA and/or NPK (1, 3, 5, 6). The primary structures of these mammalian tachykinin peptides are displayed in Fig. 1.

NPK is an N-terminally extended form of NKA and appears to be a final product of β-PPT posttranslational processing in some tissues (6–8). A comparison of the primary structure of this 36-amino acid-containing peptide from bovine (2), human (9), porcine (6), and rat (3) species reveals a striking sequence homology of 97–100%. NPK is a potent tachykinin peptide originally isolated from porcine brain (6) and appears to be differentially distributed in the central nervous system of the rat (7, 8). Tatemoto *et al.* (6) originally showed that NPK was a potent tachykinin peptide with interesting effects in a bronchoconstriction assay and on systemic arterial blood pressure. The kinetics of NPK action on these endpoints were different (i.e., a gradual onset) compared to those of either SP or NKA action. Thus, it was suggested that NPK might have different biological actions from those of SP or NKA. However, in these and other assays used by Tatemoto *et al.* (6), potency of NPK was similar to or less than the other tachykinins examined. From these studies, it is uncertain whether NPK interacts with a biological receptor that mediates SP or NKA action or whether it interacts with a receptor unique for NPK. In the current work, we demonstrate that NPK has potent effects at low doses on salivation responses in rats. Indeed, the potency of NPK exceeds that of other naturally occurring tachykinin peptides. In addition, we document that the effects of NPK on salivation are mediated by a tachykinin receptor and that NPK can potentiate the effects of SP on salivation responses in the rat.

EXPERIMENTAL PROCEDURES

Materials. SP, NKA, some lots of NPK, and [D-Pro^2,D-Trp^{7,9}]SP were from Peninsula Laboratories or Bachem, whereas another lot of NPK and β-PPT-(72–96)-peptide were prepared by the Washington University Protein Chemistry Facility. The latter two peptides were purified to >98% by HPLC. Their sequences were verified by amino acid composition analysis and primary sequence analysis on an Applied Biosystems 470 A protein sequencer. Concentrations of all peptides for biological studies were ascertained by amino acid analysis and were verified by HPLC.

[Prolyl^{3,4} (n) ^{3}H]SP ([^{3}H]SP), at a specific activity of 40 Ci/mmol (1 Ci = 37 GBq), was from Amersham. All other chemicals were from Sigma and were the highest purity available.

Salivation Bioassays. For dose–response studies, peptides (nmol/kg) were injected intravenously into the femoral vein of rats that were anesthetized with sodium pentobarbital (35 mg/kg; intraperitoneal injection). Male rats of the Sprague–Dawley strain (Holtzmann, Madison, WI; 250–300 g) were used in all experiments. Salivation bioassays were performed under a heat lamp to maintain the body temperature of anesthetized rats, and rats were tracheotomized to aid breathing. Salivary secretion was determined by examining the weight at 2-min intervals of secreted saliva as that absorbed onto cotton that was placed in the mouth for every interval as described (10).

The antagonists [D-Pro^2,D-Trp^{7,9}]SP and atropine were infused prior to salivation bioassays at a rate of 15–60 $nmol \cdot kg^{-1} \cdot min^{-1}$ and 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$, respectively. [D-Pro^2,D-Trp^{7,9}]SP and atropine were infused for a total of 5 min prior to agonist injection. All infusions were performed with a model 351 Sage infusion pump.

For studies of combined administration of NPK and SP, peptides were infused over a 10-min period. Salivation responses were determined as described above for the dose–response experiments.

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Abbreviations: SP, substance P; NKB and NKA, neurokinins B and A; β-PPT, β-preprotachykinin; NPK, neuropeptide K.

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Peptide	Sequence
Substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2
Neurokinin A	His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2
Neuropeptide K	Lys-Arg-His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2
	His-Ser-Ile-Gln-Gly-His-Gly-Tyr-Leu-Ala-Lys
	Asp-Ser-Ser-Ile-Glu-Lys-Gln-Val-Ala-Leu-Leu
	Ala-Asp
Neurokinin B	Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2

FIG. 1. Primary structures of the tachykinin peptides.

Peptide Inactivation Studies. The rates of degradation of SP and NPK by serum proteases was examined *in vitro* at 37°C at 1 μM peptide concentrations. A time course study consisting of six time points from 0 to 30 min was performed with SP and NPK. Incubations were halted with acid, and SP levels were analyzed directly while NPK was extracted according to the method of Bennett *et al.* (11). Residual SP was quantitated by RIA using a midportion directed (R-140; ref. 12) and C-terminally directed (R-5; ref. 13) SP antiserum. NPK was quantitated by HPLC using a Vydac C-4 protein/peptide column in which peptides were eluted with an acetonitrile gradient of 20–40% over 40 min in 0.2 M sodium phosphate buffer (pH 2.5) as described (13). Recovery of the highly hydrophobic NPK under these extraction conditions was >95%, while recovery of SP was >98%.

Ligand Binding Studies. The interaction of NPK and NKA with the SP-P (NK-1)-type tachykinin receptor was analyzed by displacement of [^{3}H]SP binding in submandibular gland membranes. Submandibular gland membranes were prepared and ligand binding studies were performed according to the methods of Lee *et al.* (14). Briefly, binding was performed with 0.5 nM [^{3}H]SP in 500 μl of 50 mM Tris·HCl buffer (pH 7.4) containing 3 mM $MnCl_2$, 0.02% bovine serum albumin, and ≈0.5 mg of membrane protein per ml. Bacitracin (40 μg/ml), chymostatin (4 μg/ml), and leupeptin (4 μg/ml) were included as protease inhibitors. After incubation at 20°C for 30 min, bound [^{3}H]SP was separated from free [^{3}H]SP by filtration through Schleicher & Schuell no. 32 glass fiber filters that were presoaked in 0.1% polyethyleneimine for 3 hr. Filters were washed three times with 5 ml of Tris·HCl buffer, and radioactivity was determined by liquid scintillation spectrometry. Specific binding of [^{3}H]SP was determined as the difference in total [^{3}H]SP minus that observed with 1 μM nonradioactive SP. Nonspecific binding was ≈4% of the total [^{3}H]SP binding. Peptide displacement curves were generated in which each data point represents the mean of four independent observations. The concentration of competing peptide that resulted in 50% inhibition of [^{3}H]SP specific binding (IC_{50}) was obtained from log-probit plots of the displacement data. Hill values were calculated according to the method of Levitzki (15).

RESULTS

Effects of β-PPT-Derived Peptides on Salivary Secretion in the Rat. SP has been shown previously to be a potent sialagogic peptide in the rat (16, 17), and the response is mediated by interaction of SP with an SP-P (NK-1)-type receptor in parotid and submandibular gland membranes (14, 18–21). Initially, we compared the time course of the salivation response in anesthetized rats injected intravenously with various doses of SP and with other peptides potentially derived from the β-PPT precursor. The response obtained with SP was rapid and occurred over 4–6 min (Fig. 2), with

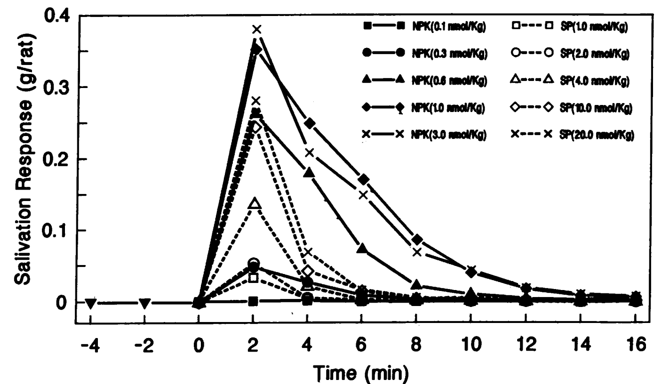

FIG. 2. Comparison of the time courses of NPK- and SP-stimulated salivary secretion. Peptides were injected intravenously into the femoral vein of rats. The spontaneous rate of salivation was 0.0007 g per 2 min.

the maximum response occurring in the initial 2-min time period. On the other hand, the response due to NPK was greater than that obtained with SP and was more prolonged in that it occurred over the 16-min time period. Dose–response curves (0.1–100 nmol of peptide per kg of body weight) for the initial (2 min) and total (16 min) salivation response were generated for NPK, SP, NKA, and β-PPT-(72–96)-peptide (Fig. 3). The initial response with NPK was some 20–30% greater than that observed with SP. The half-maximal NPK-elicited response occurred at about an 8

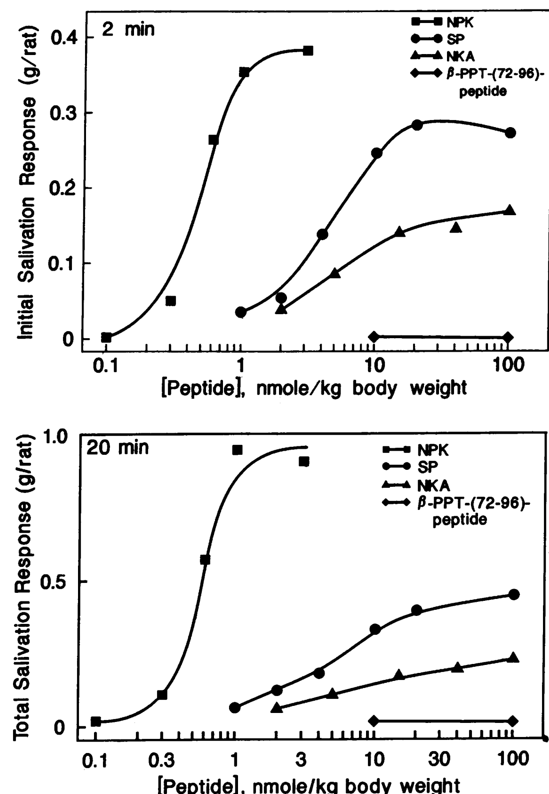

FIG. 3. Dose–response analysis of β-PPT-derived peptides on salivation responses in the rat. (*Upper*) Initial (2 min) salivation responses. Each dose–response curve represents the initial 2-min secretion of saliva by the indicated β-PPT-derived peptides. The results are the means of four or five determinations with the SEM being <20%. (*Lower*) Total (20 min) salivation responses. The data are from the same animals as in the upper figure but represent the salivation response from the 20-min time period.

times lower peptide concentration than that of SP. The total response with NPK was some 200–250% greater than that with SP, and the half-maximal response occurred at about a 10 times lower dose than that of SP. The maximal NKA-induced salivation response was much lower than that of NPK and SP and occurred at higher peptide concentrations, similar to that reported previously (10). The N-terminal region of NPK, β-PPT-(72–96)-peptide, was not active on salivary secretion (Fig. 3) nor did it antagonize the effects of NPK or SP (data not shown).

Since the potencies of NPK and SP in inducing salivation could be a result of different pharmacokinetic properties of the two peptides, we examined *in vitro* the rate of inactivation of NPK and SP by serum proteases. The estimated EC_{50} values from the dose–response data of Fig. 3 for NPK and SP on salivation are ≈0.5 nmol/kg (i.e., 0.5 μg per rat) and 4.0 nmol/kg (1.3 μg per rat), respectively. If it is assumed that the blood volume of a rat is 7% of body weight, the serum volume is 45% of the blood volume, and complete dilution of the peptides without degradation occurs, then the maximum EC_{50} values for NPK and SP effects occur at 16 nM and 130 nM, respectively. Because of the limited sensitivity of the NPK detection method, we analyzed degradation at 1 μM peptide concentration with undiluted serum *in vitro* as described in *Experimental Procedures*. Peptide degradation was rapid and the rate of inactivation of SP ($t_{1/2}$ = 3–4 min) was ≈2.5-fold greater than that of NPK (data not shown). Thus, the difference between NPK and SP salivation responses may be related in part to differential clearance of NPK and SP.

Receptor-Mediated Actions of SP and NPK on Salivary Secretion. Rat salivary gland membranes are characterized by significant numbers of tachykinin receptors of the SP-P (NK-1) type (14, 18–21), which shows a ligand selectivity of physalaemin = SP > NKA > NKB > eledoisin > kassinin. We sought to provide evidence whether the NPK-induced salivation response was due to interaction with the same receptor with which SP interacts or with a different tachykinin receptor. The tachykinin antagonist peptide [D-Pro^2,D-Trp^{7,9}]SP was used for evaluation of antagonism of NPK responses. This peptide may be a general tachykinin receptor antagonist since it antagonizes the SP-P (NK-1) type receptor (21, 22) as well as the SP-E (NK-3) type receptor (23). Fig. 4 shows that the SP-induced salivation response is antagonized by [D-Pro^2,D-Trp^{7,9}]SP but not by the cholinergic antagonist atropine, as shown previously (16, 17, 21). The NPK-stimulated salivation response was antagonized by [D-Pro^2,D-Trp^{7,9}]SP in a dose-dependent manner and also was not antagonized by atropine. These results suggested to us that NPK may be interacting with an SP-P (NK-1) type receptor or another tachykinin receptor that interacts with the [D-Pro^2,D-Trp^{7,9}]SP antagonist. It appears that inhibition of the NPK-mediated salivation response by [D-Pro^2,D-Trp^{7,9}]SP at 300 nmol/kg was somewhat greater than that observed for the SP-mediated salivation response. To test whether the NPK response could be mediated by the SP-P (NK-1) receptor, we analyzed in submandibular gland membrane preparations the displacement of [^{3}H]SP binding to the SP-P type receptor by SP, NPK, and NKA (Fig. 5). SP displaced [^{3}H]SP binding with an IC_{50} value of $9.98 \pm 1.13 \times 10^{-10}$ M and a Hill coefficient of 0.93 ± 0.03, comparable to previous studies (11, 12). On the other hand, NPK and NKA displaced [^{3}H]SP binding at IC_{50} values of $1.09 \pm 0.16 \times 10^{-7}$ M and $1.11 \pm 0.10 \times 10^{-7}$ M and Hill coefficients of 0.77 ± 0.03 and 0.75 ± 0.02, respectively. Thus, both NPK and NKA appear to interact with the SP-P (NK-1) type receptor with ≈100 times lower affinity than that of SP. It therefore appears that the salivation response induced by NPK may be mediated by the SP-P (NK-1) type receptor, or perhaps the response is mediated by an as yet uncharacterized receptor that interacts preferentially with NPK.

NPK Potentiates SP-Stimulated Salivary Gland Secretion. Since both NPK and SP stimulated salivary secretion and because both peptides may be produced as a result of posttranslational processing of the β-PPT precursor (3, 6, 7), we were interested in the effects of simultaneous administration of these tachykinins on the response. For these experiments, we used a 10-min continuous infusion paradigm rather than bolus injection to prevent complications due to secretory gland capacity. Dose–response experiments were performed with NPK and SP with the continuous infusion paradigm (data not shown). The EC_{50} values for NPK and SP occurred at 0.16 nmol·kg^{-1}·min^{-1} and 0.48 nmol·kg^{-1}·min^{-1}, respectively, and maximal responses for both peptides were similar (≈1.5 g of saliva per rat per 20 min). The salivation response due to NPK (0.08 nmol·kg^{-1}·min^{-1}) was detectable by 4 min and continued to the 14-min time point (Fig. 6 *Left*) and represented 6.5% of the maximum response. The salivation response due to SP (0.25 nmol·kg^{-1}·min^{-1}) also had similar kinetics (Fig. 6 *Left*) and represented 10.5% of the maximum response. When coinfused at these low concentrations, NPK and SP greatly stimulated secretion with the response occurring over a similar time course as either peptide alone. The total response was some 3-fold greater than the sum total of individually infused NPK or SP (Fig. 6

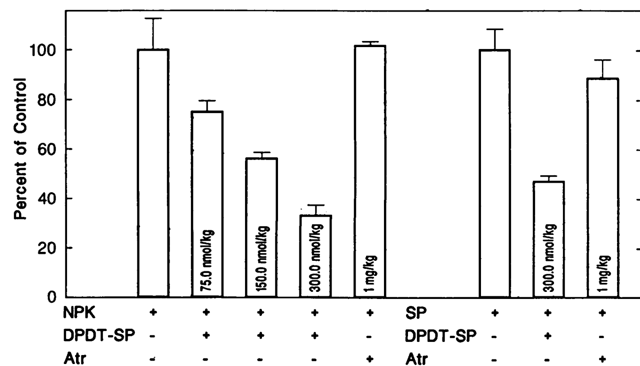

FIG. 4. Effect of cholinergic and tachykinin antagonists on NPK- and SP-induced salivation responses. Animals were treated with saline, [D-Pro^2,D-Trp^{7,9}]SP (DPDT-SP), or atropine (Atr) as shown. DPDT-SP and Atr were preinfused for 5 min at rates of 15–60 nmol·kg^{-1}·min^{-1} and 0.2 mg·kg^{-1}·min^{-1}, respectively. The doses of NPK (0.5 nmol/kg) and SP (4.0 nmol/kg) used for control injections are those that resulted in approximately half-maximum responses as shown in Fig. 3. The height of each column represents the mean percent value (±SEM) of controls in four to six determinations.

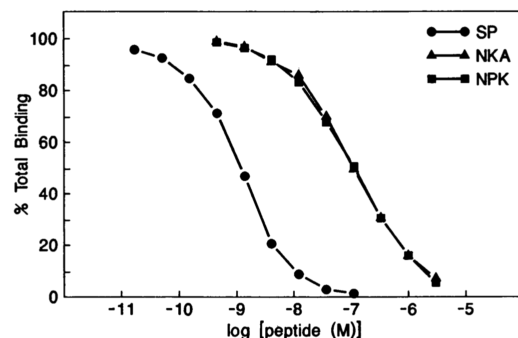

FIG. 5. Displacement of [^{3}H]SP binding to submandibular gland membranes by SP, NPK, and NKA. The binding of [^{3}H]SP to submandibular gland membranes was determined as described. The IC_{50} values for SP, NKA, and NPK were $9.98 \pm 1.13 \times 10^{-10}$ M, $1.11 \pm 0.10 \times 10^{-7}$ M, and $1.09 \pm 0.16 \times 10^{-7}$ M, respectively. Hill coefficients for SP, NKA, and NPK were 0.93 ± 0.03, 0.75 ± 0.02, and 0.77 ± 0.03, respectively.

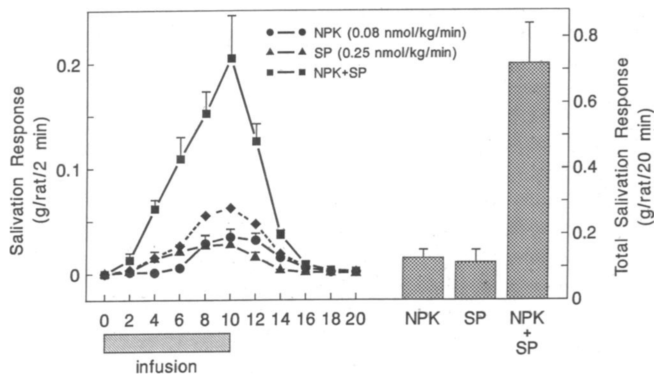

FIG. 6. Synergistic effects of NPK and SP on salivation in the rat. (*Left*) Time course of salivation responses induced by a 10-min continuous infusion of NPK, SP, and combined NPK and SP at the indicated peptide concentrations. ◆, Mathematical addition of the NPK- and SP-induced salivation response. (*Right*) Cumulative (20 min) salivation response by the indicated peptide or peptides. Salivation responses were determined as described. Each point from the time course studies, or from the total response data, is the result of six determinations and data are expressed as mean ± SEM. Peptides were administered by femoral vein infusion.

Right; $P < 0.01$, Student's t test) and represented 48% of the maximum response. Thus, NPK and SP stimulate salivary secretion in an apparently synergistic manner, indicating that these peptides may have a coordinate action on the salivary gland response and thus may be cotransmitters.

DISCUSSION

The results reported here document potent NPK-elicited responses in salivary gland tissues, which in previous studies were observed to contain tachykinin receptors predominantly of the SP-P (NK-1) type (14, 18–21). The responses elicited by NPK occurred at lower doses than those of SP (NPK $EC_{50} \cong 0.5$ nmol/kg), and the maximum response was some 2- to 2.5-fold greater than that of SP. The effects of NPK on salivation were longer lasting than those of SP and were blocked by the tachykinin antagonist [D-Pro^2,D-Trp^{7,9}]SP but not by atropine. Moreover, NPK potentiated the effects of SP on salivation. Thus, NPK appears to be the most potent sialagogic tachykinin peptide discovered to date. NPK and SP may be cotransmitters that are involved in the parasympathetic nervous system regulation of salivation.

These studies do not establish either the site or the mechanism by which NPK stimulates salivation but do provide some information on the possible peptide receptor systems involved. NPK could act directly on the salivary gland acinar cells or on the vasculature associated with these glands to alter local blood flow. Since [D-Pro^2,D-Trp^{7,9}]SP but not atropine antagonizes the salivation response induced by NPK, it would appear that the response is mediated by a tachykinin receptor. This antagonist appears to interact with more than one tachykinin receptor subtype, since it blocks tachykinin responses mediated by the SP-P (NK-1) type receptor (21, 22) as well as that by the so-called SP-E (NK-3) type receptor (23). Thus, these antagonist studies do not distinguish the type of tachykinin receptor affected. To date, a receptor that preferentially interacts with NPK has not been described (for discussion, see refs. 24 and 25). Thus, the effects of NPK could be due to its interaction with a putative NPK receptor or with the SP-P (NK-1) type receptor. Both NPK and NKA are 100 times less potent than SP in displacing [^{3}H]SP binding, whereas NPK has potent sialagogic effects and NKA is a weak sialagogue, even at high concentrations. In addition, a determination of the Hill coefficient from NPK and NKA displacement of [^{3}H]SP binding yields values of 0.77 for NPK and 0.75 for NKA, compared to a value of 0.93 for SP displacement of [^{3}H]SP binding. Thus, NPK and NKA may be interacting with a heterogeneous set of binding sites in submandibular gland membranes. Studies on the pharmacodynamics of NPK and SP inactivation in serum indicate that SP is degraded some 2.5 times faster than NPK; therefore, the high potency of NPK may not simply be due to decreased metabolism. NPK may be interacting with a specific tachykinin receptor, or it may be interacting with the SP-P (NK-1) type receptor in a different manner or with different consequences than SP. If the latter is the case, one possible explanation may relate to receptor desensitization. The SP-P (NK-1) type receptor rapidly desensitizes upon SP interaction (17, 26, 27). If NPK interacts with this receptor system, the desensitization response may be different. *In vitro* studies will be necessary to distinguish among the many possibilities concerning the site and mechanism of NPK action.

The pharmacologic effects of NPK and SP on salivation would seem to be physiologically relevant. The parotid and submandibular glands contain significant amounts of SP and presumably other tachykinin peptides derived from the PPT precursors. The peptidergic fibers in the parotid gland include as a major component those originating from the parasympathetic otic ganglion (28, 29) as well as a minor sensory component from the trigeminal ganglion (29). The peptidergic fibers in the submandibular gland also appear to have multiple origins; the majority of peptidergic fibers were originally believed to be intrinsic to the gland (28, 30, 31), but on the basis of recent experiments, tachykinin innervation appears to arise from the diffuse submandibular ganglion cells within the hilum of the submandibular gland (28), while a minor component may be of sensory origin (31). Submandibular gland SP may be derived from the preganglionic parasympathetic chorda tympani (30), although this has not been substantiated in recent experiments (28, 31). It has previously been shown that electrical stimulation of the parasympathetic nerve supplying the parotid gland results in atropine-resistant salivary secretion (32), and a decrease in the content of SP (as well as that of vasoactive intestinal polypeptide) in the glandular postganglionic nerve fibers occurs as a result of peptide release (33). In preliminary experiments, we have detected immunoreactive NPK in salivary gland extracts by a combined HPLC radioimmunoassay with a NKA antiserum (unpublished data). The synergistic effects of SP and NPK on salivary secretion may be clinically important since patients with malignant carcinoid tumors express SP, NPK, and to a lesser extent NKA in relatively high amounts (34–38). In this regard, it is of interest that hypersalivation has been observed in a patient diagnosed with metastatic laryngeal carcinoid tumor in which there was ectopic production of SP and NPK (39), both of which may have contributed to the hypersalivation.

Neurotransmitter coexistence has been observed in many central and peripheral systems and includes both classical transmitter–peptide coexistence and peptide–peptide coexistence (40, 41). For classical transmitter–peptide coexistence, two previous examples of coexistent transmitters with synergistic effects on salivation deserve comment. Lundberg and coworkers (42, 43) have shown that combined administration of the coexistent parasympathetic transmitters acetylcholine and vasoactive intestinal polypeptide in the cat synergistically stimulate salivation, with acetylcholine primarily eliciting the secretory response and vasoactive intestinal polypeptide regulating the vasodilatory response. On the other hand, norepinephrine and neuropeptide Y coexist in the cat superior cervical sympathetic ganglia as well as in nerve terminals derived from the ganglia (44). Local infusion of norepinephrine or neuropeptide Y alone caused a partial vascular response for each (i.e., norepinephrine caused

vasoconstriction and secretion, and neuropeptide Y caused vasoconstriction but no secretion). The combined local infusion of norepinephrine and neuropeptide Y bring about a vasoconstriction response in the submandibular gland that is similar to sympathetic nerve stimulation (45).

Peptides derived from separate genes, as well as peptides derived from a single gene, comprise the types of peptides known to coexist. For coexistent peptides derived from the same gene, two situations of synergism seem to be relevant for comparison with the current studies. For example, corticotropin and melanocyte-stimulating hormone derivatives coexist within the proopiomelanocortin precursor (46). A melanocyte-stimulating hormone-related peptide (termed γ_3-MSH) by itself stimulates adrenal cortex cholesterol ester hydrolysis and also synergistically potentiates corticotropin stimulation of corticosterone and aldosterone biosynthesis (47), presumably by acting via distinct receptors. On the other hand, vasoactive intestinal polypeptide and a peptide with N-terminal histidine and C-terminal isoleucine, homologous peptides coexpressed in the vasoactive intestinal polypeptide precursor (48), stimulate prolactin secretion additively at submaximal doses (49) via actions through the same receptor (50). Although α-, β-, and γ-PPT precursors differentially encode the three tachykinin peptides SP, NKA, and NPK (2, 3), the functional significance of this coexistence has been uncertain since there appears to be a mismatch between the tachykinin peptides SP and NKA and the receptors with which they are believed to interact (25, 51–53). Moreover, it has been difficult to demonstrate significant amounts of NKA (NK-2) receptors in the central nervous system (25). The preprotachykinin precursors may well be polyproteins in that not only the tachykinin-encoding regions but possibly other conserved regions of these precursors may harbor biologically active peptides that may interact with physiological receptors throughout the nervous system. These receptors for tachykinin precursor peptides may be differentially expressed such that selectivity of tachykinin responses resides with the specific type of receptor expression. It is clear from this and other studies (6), however, that NPK is a potent tachykinin in the rat, and the apparent synergistic effects of NPK and SP indicate that these peptides may be cotransmitters in tachykinin-mediated events in certain nervous system structures.

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