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NEUROPEPTIDE Y DECREASES RECTAL TEMPERATURE AFTER INTRACEREBROVENTRICULAR ADMINISTRATION IN CONSCIOUS DOGS

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INDEXING WORDS

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SYNOPSIS

Effects of intracerebroventricular (i.c.v.) administration of neuropeptide Y (NPY), peptide YY (PYY) and pancreatic polypeptide (PP) on thermoregulation were studied and compared with those of several neuropeptides such as thyrotropin releasing hormone (TRH), cholecystokinin-octapeptide (CCK-8) and vasoactive intestinal peptide (VIP). Mongrel dogs were prepared with a chronic cannula allowing i.c.v. infusion into the lateral ventricle. Changes in rectal temperature were measured for 3 hours after physiological saline (100μl) or appropriate doses (1.19nM or less) of PP family peptides as well as 1.19nM TRH, CCK-8 and VIP administration.

Control saline infusion slightly decreased rectal temperature. NPY and PYY (1.19nM) produced a rapid onset of hypothermia, which was significantly different from the rectal temperature of saline treated dog, and then an increase to above the baseline temperature was observed within 2 hours. However, the fact that PP

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did not show hypothermic effects, may suggest that NPY and PYY are more intimately related to each other than PP in biologic actions as well as in sequence homology. TRH and CCK-8 produced sustained hyperthermia which was associated with shivering, whereas VIP failed to affect body temperature. Salivation, vomiting, polypnea, urination, and/or groaning were often evoked by TRH but scarcely elicited by CCK-8. NPY produced no significant change in gross behavior or blood pressure. The present results indicate that NPY might be a possible mediator of mammalian thermoregulation, and needs further evaluation.

INTRODUCTION

Recently, Tatemoto et al. have isolated pancreatic polypeptide (PP) family brain-gut peptides, neuropeptide Y (NPY) and peptide YY (PYY), from porcine brain and intestine, respectively.[26, 27, 28, 29] NPY is known to be widely distributed throughout the mammalian central and peripheral nervous system, and extracted in concentrations higher than those of any other peptide hitherto discovered in the brain.[1, 4] However, the physiological role of NPY in the central nervous system is not fully understood, and little is known about its effects on thermoregulatory functions. The present study was performed to investigate the thermoregulatory effects of NPY as well as PP and PYY in view of structure-activity relationships in conscious canine. Furthermore, several neuropeptides such as thyrotropin releasing hormone (TRH), cholecystokinin-octapeptide (CCK-8) and vasoactive intestinal peptide (VIP) were studied and compared for their thermoregulatory effects. Preliminary studies have been published in abstract form.[20]

MATERIALS AND METHODS

Animal preparation

Six adult mongrel dogs, weighing about 12kg, were used in all studies. They were anesthetized with sodium thiamylal and settled with a chronic cannula allowing intracerebroventricular (i.c.v) infusion. The tip of a 20-gauge stainless steel tube was stereotactically implanted into the lateral cerebral ventricle at

approximately 20mm anterior to the interaural line, 8mm lateral to the midline and 15mm to the dorsal aspect of the brain. The methods used have been described elsewhere.[5] The patency of the ventricular cannula was confirmed before and after each experiment by observing good efflux of clear cerebrospinal fluid (CSF). At the end of all experiments animals were sacrificed and it was also confirmed that the cannula was squarely within the lateral cerebral ventricle and that the track of the implanted cannula was attended by no fissure formation.

Experimental design

The dogs were allowed to recover 2 weeks before experimentation and housed with controlled lighting (on from 0600 to 1800 hr) at an environmental temperature of 22 ± 2C until they were used. The animals were fasted for 16 hr and placed in a jacket. All experiments were carried out between 0900 and 1500 hr in a fully conscious, relaxed state. Rectal temperature (Tre) was measured via a thermistor (Nihon Kohden, Japan) inserted 10cm beyond the anus. The peptides dissolved with 100μl 0.9% saline or saline alone as control were infused intracerebroventricularly for 5 min aseptically, and Tre was measured at 5 min intervals over the next 3 hr. The peptides used were: porcine NPY, PP and PYY at doses of 0.5-5μg; 0.43μg of TRH, 1.36μg of CCK-8 and 4μg of VIP, equimolar of 5μg (1.19nM) of PP family peptides. NPY and PYY were kindly donated by Dr. K. Tatemoto of Stanford University, U.S.A., and PP was a generous gift from Dr. R.E. Chance of Lilly Research Laboratories, Eli Lilly and Co., U.S.A. VIP and CCK-8 were kindly donated by Dr. N. Yanaihara of Shizuoka College of Pharmacy, Japan. TRH was obtained from Tanabe Seiyaku Co., Ltd., Japan.

Analytical methods

Rectal temperature after i.c.v. administration of peptides or saline was shown as changes from the baseline temperature. All results were expressed as mean ± SEM. Temperature response to peptide administration was compared with that to saline vehicle and assessed by the Student's t-test. P-values of <0.05 were considered significant.

RESULTS

Animals with i.c.v. administration of saline exhibited a small but significant decrease in Tre from 50 to 115 min ($P < 0.05$, data is not shown) despite the 1-2 hr stabilization period before experimentation. Animals without saline administration also showed a decrease in Tre, suggesting that this might be in a part due to circadian variation in Tre. Accordingly, results were also expressed as changes from that found after i.c.v. saline administration.

Five μg (1.19nM) of NPY produced a more rapid onset of decrease in Tre followed by an increase to above the baseline level (Fig. 1). This temperature response was significantly different from controls from 30 to 40 min (ΔTre = -0.11 ~ -0.12C, $P < 0.05$). and from 165 to 180 min (ΔTre = +0.25 ~ +0.31C, $P < 0.05$). PYY also showed hypothermic effects (Fig. 2) which were significant from 55 to 70 min when compared with saline-treated controls (ΔTre = -0.14 ~ -0.19C, $P < 0.05$). This lower temperature returned to and above the baseline level within 2 hours. However, i.c.v. administration of PP did not cause a significant decrease of body temperature (Fig. 3).

Figure 4 and 5 depict the temperature response elicited by different doses, 5, 1.5 and 0.5μg, of NPY and PYY, respctively. In both NPY- and PYY-treated animals, the most significant effect was observed at the highest dose but dose-dependency was not clearly demonstrated. NPY at a dose of 5μg did not appreciably alter gross behavior or blood pressure.

As can be seen in Fig. 6, i.c.v. administration of several neuropeptides such as TRH, CCK-8 and VIP (1.19nM) exerted variable influences on thermoregulation as well as on other vegetative functions. TRH (0.43μg)-treated animals developed hyperthermia; this was statistically significant from 70 to 105 min when compared with controls (ΔTre = +0.30 ~ +0.34C, $P < 0.05$). TRH has frequently been noted to have a general excitant action (including shivering) as well as profuse salivation. Other effects noted were: groaning, polypnea, urination and/or vomiting. Hyperthermia was also observed in animals receiving CCK-8 (1.36μg). CCK-8 caused a steady and sustained rise in Tre which was significant from 30 to 180 min (ΔTre = +0.32 ~ 0.48C, $P < 0.05$). Development

of hyperthermia was associated with shivering and other minor behavioral changes including licking. On the contrary, 4μg of VIP failed to affect body temperature and did not produce behavioral changes.

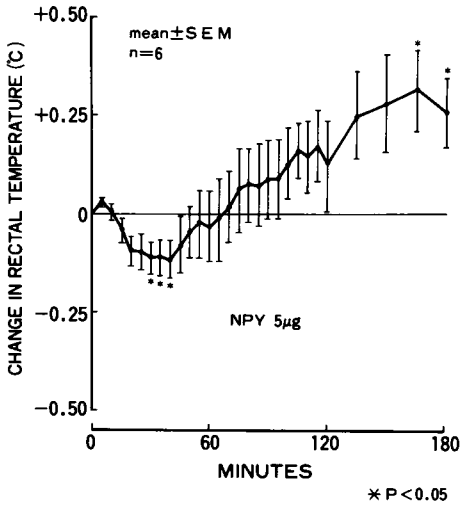

Fig. 1
Change in rectal temperature following intracerebroventricular infusion of 5μg of NPY; data are shown as changes from rectal temperature following intracerebroventricular saline administration at each time point.

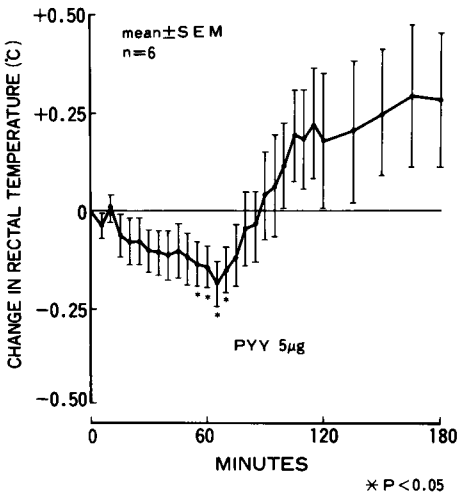

Fig. 2
Change in rectal temperature following intracerebroventricular infusion of 5μg of PYY; data are shown as changes from rectal temperature following intracerebroventricular saline administration at each time point.

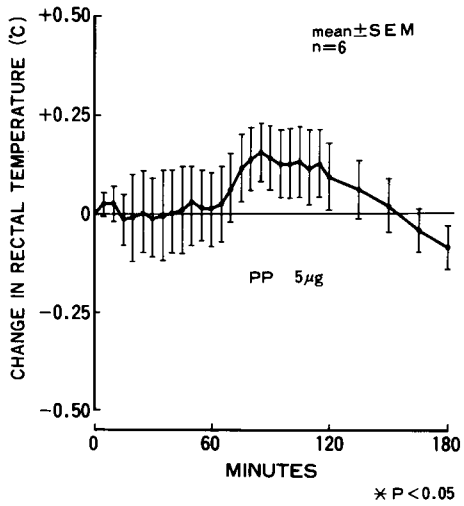

Fig. 3
Change in rectal temperature following intracerebroventricular infusion of 5μg of PP; data are shown as changes from rectal temperature following intracerebroventricular saline administration at each time point.

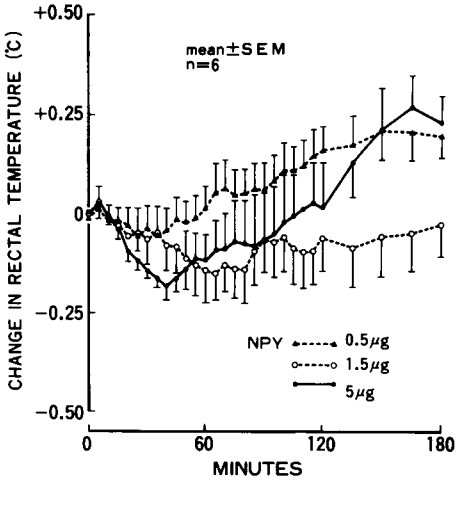

Fig. 4
Change in rectal temperature following intracerebroventricular infusion of three doses of NPY (0.5, 1.5 and 5μg).

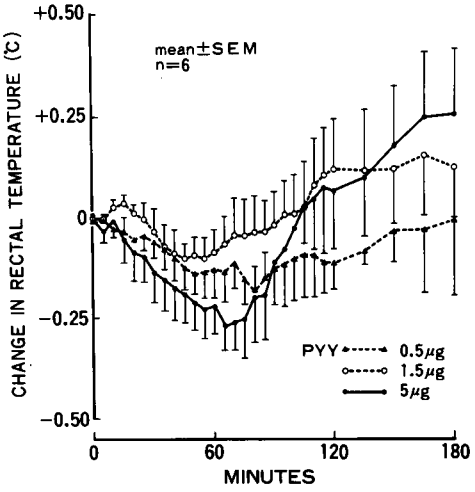

Fig. 5
Change in rectal temperature following intracerebroventricular infusion of three doses of PYY (0.5, 1.5 and 5μg).

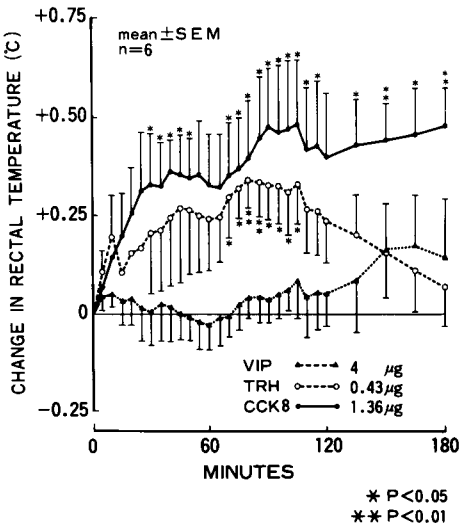

Fig. 6
Change in rectal temperature following intracerebroventricular infusion of TRH, CCK-8 and VIP in the same molar dose (1.19nmol); data are shown as changes from rectal temperature following intracerebroventricular saline administration at each time point.

DISCUSSION

The present experiment showed that 5μg of NPY infused into the lateral cerebral ventricle of conscious canine decreased the rectal temperature significantly at an environmental temperature of 22 ± 2C. NPY seems to induce a biphasic effect of hypothermia first and then hyperthermia, although dose-dependency is not clearly demonstrated. PYY also induced more potent and prolonged hypothermia than NPY, whereas administration of PP in the same dogs did not alter the rectal temperature significantly. Thus, the PP family peptide differed markedly in hypothermic potency as well as in vasoconstrictive potency.[17] Apart from these thermoregulatory actions, NPY produced no significant change in gross behavior or blood pressure.

NPY-like immunoreactivity is known to be localized throughout the brain,[9, 10] and especially high concentrations have been measured in the hypothalamus by radioimmunoassay.[1, 4] Receptors for NPY are also present in brain synaptosomes[25] with particularly high concentrations in the hypothalamus,[30] suggesting that NPY might have a role in the modulation of various hypothalamic functions. NPY may affect secretion of luteinizing hormone[13, 19] as well as adrenocorticotropic hormone[11] and be involved in neural regulation of feeding behavior[6] and circadian rhythms.[2, 3] Our present findings suggest that thermoregulatory functions should be added to the list of NPY actions. NPY actually inhibits prostaglandin E_2 induced fever without increasing respiratory frequency and peripheral (skin) blood flow (A. Inui, unpublished data).

It is well known that NPY co-exists with catecholamines in both the central and the peripheral nervous system.[9, 10, 17] NPY appears to be located in certain brainstem noradrenergic and adrenergic nuclei that project to the hypothalamus and also in intrinsic hypothalamic neurons.[9, 10, 25] Sympathetic activation induces co-release of NPY and noradrenaline; these two agents cooperate subsequently in functional responses such as vasoconstriction.[18] There is reasonable evidence for the role of catecholamines in the mediation of the preoptic anterior hypothalamic mechanism for acceleration of heat loss, blockade of heat production, or both simultaneously.[22] Thus, one possible explanation

other than singlehanded action of NPY on thermoregulation is that NPY might act in concert with catecholamines to decrease body temperature. Another possibility is that NPY's hypothermic activity might be mediated by the effect of ACTH on thermoregulation. We have recently shown that NPY stimulates ACTH-cortisol secretion dose-dependently after intracerebroventricular administration.[11] Much of the current research suggests that ACTH and the shorter molecule -MSH may have roles in physiological control of body temperature.[7, 15] The naturally occurring release of ACTH during fever might be important to fever control by virture of an action of the peptide on central temperature control. However, ACTH is not primarily concerned with the hypothermic effect of NPY, since PP which also stimulates ACTH secretion[11] did not show a hypothermic effect.

In this study we showed that several other neuropeptides located in the hypothalamus could serve as neurochemical intermediaries involved in temperature regulation.

TRH, a tripeptide known for its neuroendocrine effects on TSH and prolactin, usually induces a short lasting increase in temperature,[7] although cats respond with hypothermia.[23] We observed that central administration of TRH resulted in hyperthermia in awake dogs. TRH caused both general excitant action that would tend to raise temperature by increasing heat production and heat loss effector activity such as polypnea and salivation. These findings suggest that the major action of TRH at the level of thermoregulatory effectors is primarily to increase heat production.

CCK-8 has been reported to induce hypothermia in rats[14, 21] and rabbits[16] after lateral ventricular injection. However, we observed sustained hyperthermia after administration which was greater than that produced by TRH. This implies great species differences in the ability of different animals to modify body temperature in response to peptide administration. The thermal effects of CCK-8 were accompanied by minor autonomic changes, unlike those of TRH, suggesting that hyperthermia following CCK-8 adminstration is not due, solely, to secondary non-specific effects.

Only limited results have been reported concerning the thermoregulatory role of another biologically active hypothalamic

peptide VIP. In the cat an intraventricular injection of VIP in high concentration evokes a rapid, albeit brief, hyperthermic response which is associated with the concomitant signs of heat production such as shivering.[28] The hyperthermic effect of VIP was also shown in the rat.[12] However, 4μg of VIP failed to affect body temperature in the present study using dogs.

There are a number of variables which might be involved in the chemical manipulation of the brain.[22] Temperature response to central administration of putative neurotransmitters will depend upon the site of application, the dose given, the volume or PH of the carrier vehicle, the environmental temperature, the confounding effect of an anesthetic, or the species used. Each of these factors might be crucial to an interpretation of a temperature response. Rectal temperature might be also a poor index of real body temperature. It is necessary, therefore, to test the generality of the results obtained and to delineate the physiological role of neuropeptides during thermoregulating processes. Furthermore interactions of neuropeptides would be another important issue for future study.

In conclusion, our results presented here suggest that NPY should be considered as a possible candidate peptide involved in the neuromodulation of thermoregulation. The precise mechanism of action and the physiological role of this peptide in thermal homeostasis remain to be established.

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