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Effects of Peripheral Neurotensin on Behavior of the Rat

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SANDOVAL, S. L. AND P. J. KULKOSKY. *Effects of peripheral neurotensin on behavior of the rat.* PHARMACOL BIOCHEM BEHAV **41**(2) 385–390, 1992.—Neurotensin (NT), a tridecapeptide found in brain and gut neurons, inhibits feeding and grooming, increases drinking, and enhances ethanol-induced sedation in rats after central injection. We tested the behavioral effects of IP injection of NT (0.1–100 μg/kg) in water-deprived rats given access to 5 or 10% ethanol for 30 min, followed by 30-min access to water. Behaviors during alcohol access were quantified with an instantaneous time-sampling observational technique. Food intake and observed feeding and grooming behaviors were significantly inhibited by large doses of NT (10–100 μg/kg) and water intake and resting behavior were increased. When the "limited access procedure" was used to induce ethanol selection in nondeprived rats, NT did not affect ethanol or water intake. Peripheral NT affects intake of food and water and observed feeding, grooming, and resting after peripheral injection in deprived rats, but does not affect ethanol consumption. These actions suggest physiological roles for endogenous neurotensin and its receptors in regulation of specific behaviors.

Neurotensin Ethanol intake Food intake Water intake Grooming Resting
Limited access procedure

NEUROTENSIN (NT) is a tridecapeptide (pyro Glu-Leu-Try-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH) found throughout the central and peripheral nervous systems and in the gastrointestinal tract. NT was first isolated from bovine hypothalamic extracts by Carraway and Leeman in 1973 (7). NT has since been shown to decrease food intake after injection in the following locations: paraventricular nucleus, ventral tegmental area, ventromedial nucleus of the hypothalamus, substantia nigra, nucleus of tractus solitarius, and cerebral ventricles (3,20,21,23,24,32,36,44,48,50). Both norepinephrine- and dynorphin-induced feeding were suppressed by NT given into the paraventricular nucleus or ICV (32,49). NT given intracranially decreased spontaneous motor activity and ethanol- or dopaminergic agent-induced locomotor activity in rats and enhanced ethanol- or barbiturate-induced impairment and sedation (9,11–13,15,16,25,26,34,35,37,40–42, 46,51,58). Spontaneous grooming and grooming induced by substance P, bombesin, ACTH, TRH, novelty, or water immersion was suppressed by ICV NT (10,29,52–57,59). Also, water intake, locomotion, rearing, sniffing, and catalepsy were each shown to increase after specific central administration of NT in the rat (2,5,22,28,47). Finally, centrally administered NT reduced responsiveness to pain (8,9,27,43), altered conditioned avoidance behaviors (38,56), and supported self-injection responses when delivered to the ventral tegmental area (19).

However, there are fewer studies of the effects of peripherally administered NT on behavior. High IV doses of NT reduced feeding and increased water intake in rats (48), while in dogs an area postrema-dependent emesis was induced (6). There are few reports of the effects of IP administration of NT on behavior, although IP NT was noted to inhibit food intake (18). Therefore, to add to this knowledge, we tested the behavioral effects of intraperitoneal injections of a wide range of doses of NT. To examine our hypothesis of possible brain-gut neuropeptidergic control of ethanol consumption and associated behaviors (30), we used a valid and reliable observational technique (1,18) to test NT's potential influence on alcohol intake-related behaviors in water-deprived and nondeprived rats in forced- and free-choice tests. Results will allow a characterization of the short-term behavioral effects of IP NT in water-deprived and ad lib rats with access to ethanol, water, and food.

METHOD

Animals

Subjects were 36 Wistar rats (*Rattus norvegicus*), 24 males and 12 females (outbred, Charles River Crl: [WI]BR). All

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animals had ad lib access to Purina Rodent Laboratory Chow (5001) in stainless steel hoppers. They were individually housed in wire-mesh stainless steel cages with a 12L:12D lighting cycle (0700–1900 light, unless otherwise specified) in a room with an ambient temperature of approximately 23°C. Stainless steel rubber-stopper protection rings were mounted at the center front of each cage. Calibrated 50-ml polycarbonate centrifuge tubes were fitted with rubber stoppers and 4-in. bent valveless stainless steel spouts and were inserted into openings in the protection rings for the presentation of 3, 5, 6, or 10% w/v ethanol solutions (from U.S.P. 95%/deionized water) or water.

Procedure

Water deprivation. Initially, 12 male rats were deprived of water for 23 h but food remained ad lib. At 1200, they were taken from their cages, weighed, returned, and then given access to 5% ethanol for 30 min followed by access to deionized water for 30 min. Fluid intakes were measured to the nearest 0.5 ml. Food was weighed to the nearest 0.01 g at 30- and 60-min intervals. Intakes were corrected for spillage of food, which was caught on paper towels placed beneath the cages and also measured to the nearest 0.01 g. Rats' behaviors were quantified with an instantaneous time-sampling observational method originally described by Gibbs and colleagues (1,18). Behaviors were observed and categorized during a tone-cued 0.6-s interval, once each minute for the first 30 min. Categories included drinking, resting, feeding, grooming, standing, rearing, and other behaviors. After 5 days' adaptation to this procedure, rats were given 1 ml/kg IP injections of 0.9% w/v NaCl (saline) immediately prior to ethanol access on the sixth day. The rats received individually randomized sequences of IP injections of 0, 0.1, 1, 10, and 100 μg/kg neurotensin (Bachem. Inc., Torrance, CA, Lot #A 13751) immediately (within 1 min) prior to ethanol access on five consecutive days (days 7–11), with the restriction that all rats receive all doses.

In a second phase of this experiment, the above-described procedure was replicated commencing 19 days after completion of the first phase, with the exception that 10% ethanol was presented instead of 5%.

Limited access procedure. A design called the "limited access procedure" [LAP (33,39)] was used to induce alcohol intake in nondeprived rats. Twenty-four ad lib fed and watered rats were housed in separate rooms, 6 females and 6 males in each room, with a 12L:12D lighting cycle changing at 0700 to either 12 h dark ("dark" room) or 12 h light ("light" room). At 1100, they were moved from their home cages to individual experimental cages placed 3.5 feet across the room. Animals were given 9 days of a two-bottle choice of 3% ethanol or water for 40 min, and then 6% ethanol or water for 8 days, with 3 days of saline injection (1 ml/kg) immediately before fluid access in the latter phase. Relative (left–right) placement of the ethanol and water tubes in the experimental cages was initially randomized and then alternated daily thereafter. At the conclusion of the 40-min access period, consumption of both ethanol solution and deionized water was measured to the nearest 0.5 ml and the animals were returned to their home cages with ad lib food and water.

All data were analyzed with split-plot and repeated measures of analyses of variance (ANOVA's) followed by Duncan's multiple-range test at an alpha significance level of $p < 0.05$.

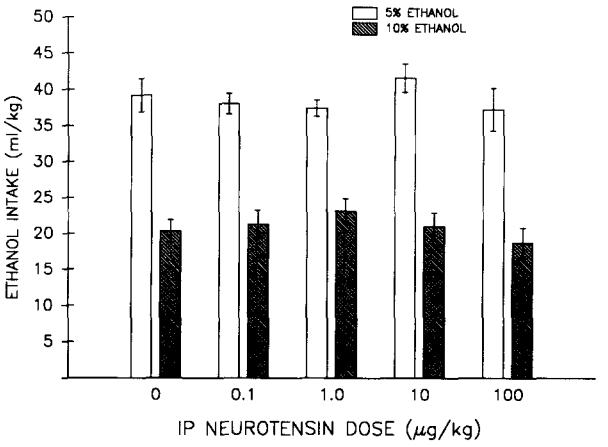

FIG. 1. Mean (± SE) 5 and 10% ethanol intake (ml/kg) as a function of IP dose of NT (0–100 μg/kg) in water-deprived rats in a 30-min session.

RESULTS

Water Deprivation

Mean (±SE) intake of 5 and 10% ethanol of water-deprived rats 0–30 min after IP injection of doses of neurotensin is shown in Fig. 1.

Analysis indicated only a significant main effect of ethanol concentration on ethanol intake, $F(1,11) = 318.7$, $p < 0.05$, as rats consumed more 5% ethanol than 10% ethanol. The effect of NT, $F(4,44) = 0.95$, and the interaction of NT and ethanol concentration, $F(4,44) = 0.84$, were not statistically significant (p's > 0.05).

Mean (±SE) intake of water of water-deprived rats 30–60 min after access to 5 or 10% ethanol and IP doses of neurotensin is shown in Fig. 2. There were significant ($p < 0.05$) main effects on water intake of ethanol concentration, $F(1,11) = 102.65$, and NT dose $F(4,44) = 4.3$, but the interaction was not significant, $F(4,44) = 1.06$, $p > 0.05$. Posthoc analyses revealed a reliable increase in water intake after 100 μg/kg NT in rats with prior access to 10% ethanol.

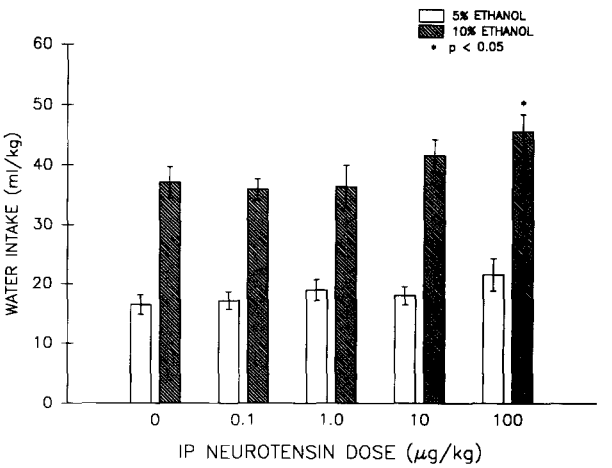

FIG. 2. Mean (±SE) water intake (ml/kg) as a function of IP dose of NT at 30–60 min after access to 5 or 10% ethanol.

Mean (±SE) intake of food of water-deprived rats with access to 5 or 10% ethanol, at 0–30 and 30–60 min after injection of IP doses of neurotensin, is shown in Fig. 3. Analysis revealed significant ($p < 0.05$) main effects on food intake of ethanol concentration, $F(1,11) = 7.8$, and dose of neurotensin $F(4,44) = 4.39$, as rats consumed more food when given 5% ethanol than when given 10% ethanol, and NT reduced food intake. The interaction of ethanol concentration and time period was statistically significant, $F(1,11) = 19.37$, as rats with access to 5% ethanol reduced food intake across time intervals, unlike rats with 10% ethanol. The interaction of ethanol concentration and dose of NT was statistically significant, $F(4,44) = 3.88$, as NT more strongly affected food intake associated with 5% ethanol than with 10% ethanol. Posthoc comparisons of means revealed that NT significantly reduced food intake associated with 5% ethanol at doses of 10 and 100 μg/kg and reduced food intake associated with 10% ethanol at 100 μg/kg at 0–30 min after injection.

Analysis of observed ethanol drinking behavior indicated only a significant main effect of ethanol concentration, $F(1,11) = 40.98$, $p < 0.05$, as rats presented 5% ethanol were observed drinking more often than rats with 10% ethanol. The effect of neurotensin, $F(4,44) = 0.623$, $p > 0.05$, and the interaction of NT and ethanol concentration, $F(4,44) = 0.92$, $p > 0.05$, were not significant. This pattern of results paralleled the pattern seen in analysis of ethanol intake data depicted in Fig. 1.

Mean (±SE) counts of observed feeding behavior of water-deprived rats with access to 5 or 10% ethanol after IP doses of neurotensin is shown in Fig. 4. Statistical analysis revealed significant ($p < 0.05$) main effects on feeding of ethanol concentration, $F(1,11) = 19.64$, and dose of NT, $F(4,44) = 3.55$, as rats with access to 5% ethanol were observed feeding more often and NT reduced feeding behaviors. The interaction of these factors was not statistically significant, $F(4,44) = 2.04$, $p > 0.05$. A posthoc inspection of means indicated reliable decreases in observed feeding at a dose of 100 μg/kg NT in rats with access to 10% ethanol. When data were analyzed in 5-min blocks, cumulative feeding observations were significantly reduced relative to saline control at 15–30 and 25–30 min after NT injection at doses of 10 and 100 μg/kg, respectively, during 5% ethanol access and at 5–30 min after injection at 100 μg/kg during 10% ethanol access.

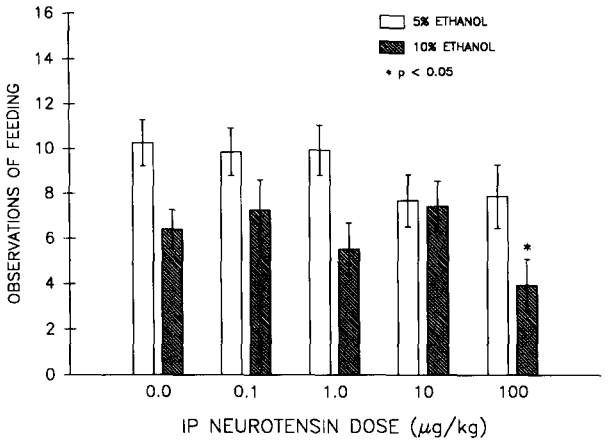

FIG. 4. Mean (±SE) observations of feeding behavior as a function of IP dose of NT in rats with access to 5 or 10% ethanol.

Mean (±SE) counts of observed grooming behaviors of rats with 5 or 10% ethanol after IP doses of NT is shown in Fig. 5. There was a significant ($p < 0.05$) main effect of dose of NT on grooming, $F(4,44) = 4.97$, and an interaction of ethanol concentration and NT dose, $F(4,44) = 3.07$. Comparison of means showed that observed grooming was reduced by NT at doses of 0.1, 10, and 100 μg/kg in rats with 10% ethanol.

Mean (±SE) counts of observed resting behavior of rats with 5 or 10% ethanol after IP doses of NT is depicted in Fig. 6. There were significant ($p < 0.05$) main effects of ethanol concentration, $F(1,11) = 13.14$, and NT dose, $F(4,44) = 5.01$, on resting behavior, but the interaction was not significant, $F(4,44) = 0.71$, $p > 0.05$. Rats receiving 10% ethanol rested more often, and there was a reliable increase in resting at 100 μg/kg NT when 10% ethanol was available. Analysis of data in 5-min time blocks revealed increases in cumulative resting counts at 20–30 min after injection of 100 μg/kg NT when 5% ethanol was presented, and at 10–30 min after injection of that dose of NT when 10% ethanol was available.

There was a significant main effect of ethanol concentration on standing behavior, $F(1,11) = 12.92$, $p < 0.05$, as rats

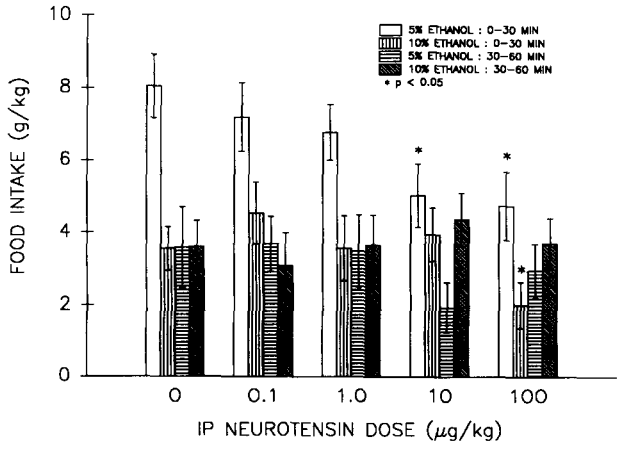

FIG. 3. Mean (±SE) food intake (g/kg) as a function of IP dose of NT at 0–30 and 30–60 min after access to 5 or 10% ethanol.

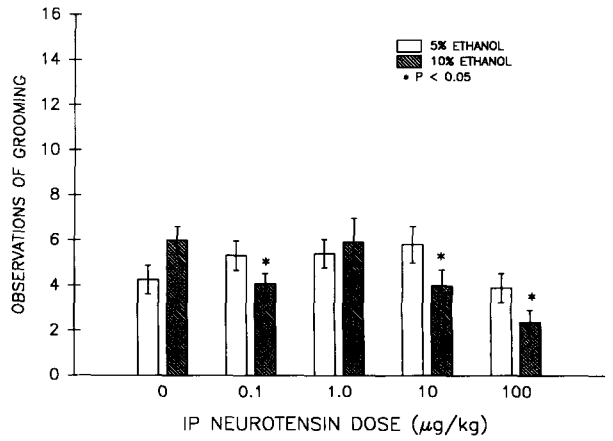

FIG. 5. Mean (±SE) observations of grooming behavior as a function of IP dose of NT in rats with access to 5 or 10% ethanol.

with 10% ethanol access were observed in stationary, nonresting positions more often than rats with 5% ethanol (respective grand means = 6.6 and 3.9 counts). The effect of neurotensin on standing behavior, $F(4,44) = 0.63$, and the interaction of NT and ethanol concentration, $F(4,44) = 0.1$, were not significant, (p's > 0.05).

Other categories of behavior, comprising rearing, sniffing, locomotion, and eating feces, were only infrequently observed so these counts were combined into a single category denoted "other behavior." Analysis of this combined category indicated a significant main effect of ethanol concentration, $F(1,11) = 7.3$, $p < 0.05$, as rats with 10% ethanol exhibited more other behaviors than rats with 5% ethanol (respective grand means = 1.6 and 1.1 counts). Neither the main effect of NT on other behaviors, $F(4,44) = 2.05$, nor the interaction of NT and ethanol concentration, $F(4,44) = 0.24$, was reliable (p's > 0.05).

Limited Access

Mean (±SE) intake of 6% ethanol and water of nondeprived rats given two-bottle access during the light or the dark phase of the lighting cycle is shown in Figs. 7 and 8, respectively, as a function of IP dose of neurotensin. Four-way analysis revealed significant ($p < 0.05$) main effects of sex, $F(1,20) = 12.45$, and fluid type, $F(1,20) = 31.65$, as females had larger intakes than males and ethanol solution was preferred to water. The main effects of lighting phase, $F(1,20) = 0.26$, and neurotensin dose, $F(4,80) = 1.15$, were not statistically significant (p's > 0.05). The interaction of sex and lighting phase, $F(1,20) = 15.12$, and the interaction of lighting phase, sex, and fluid type, $F(1,20) = 7.61$, were statistically significant, as females displayed greater mean fluid intake in the dark phase than in the light phase (grand means, 7.71 vs. 4.64 ml/kg, respectively), unlike males (grand means, 2.53 vs. 4.89 ml/kg, respectively). The sex difference in response to lighting cycle was more pronounced with ethanol intake as females consumed an average of 11.04 ml/kg in the dark and 6.34 ml/kg in the light, while male means were 2.71 and 7.05 ml/kg, respectively, whereas females consumed 4.37 and 2.94 ml/kg of water in dark and light, respectively, while males consumed 2.35 and 2.73 ml/kg of water, respectively. No other two-way, three-way, or four-way interaction

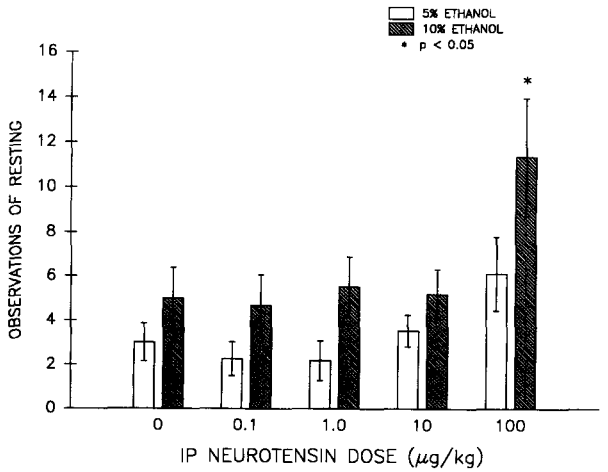

FIG. 6. Mean (±SE) observations of resting behavior as a function of IP dose of NT in rats with access to 5 or 10% ethanol.

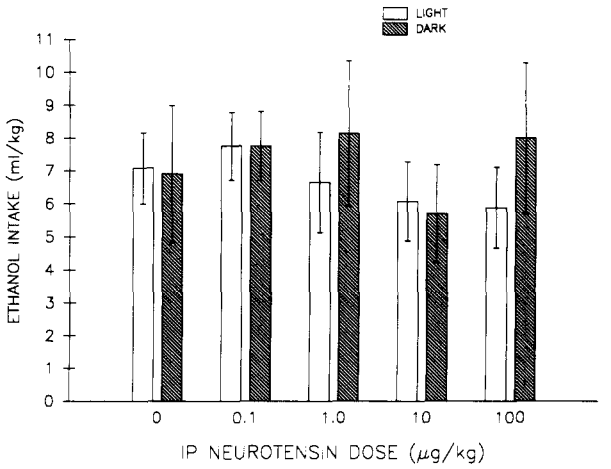

FIG. 7. Mean (±SE) ethanol intake (ml/kg) of nondeprived rats as a function of IP dose of NT during light or dark phase of the lighting cycle in the limited access procedure (LAP).

was statistically significant (p's > 0.05), that is, lighting phase × fluid type, $F(1,20) = 0.07$; sex × fluid, $F(1,20) = 4.22$; phase × dose, $F(4,80) = 1.32$; sex × dose, $F(4,80) = 0.53$; fluid × dose, $F(4,80) = 1.18$; phase × sex × dose, $F(4,80) = 2.04$; phase × fluid × dose, $F(4,80) = 0.76$; sex × fluid × dose, $F(4,80) = 0.50$; and phase × sex × fluid × dose, $F(4,80) = 2.08$.

DISCUSSION

Our data show that peripherally injected neurotensin decreases food intake, feeding behavior, and grooming and increases water intake and resting behavior in the male rat. However, ethanol intake was not affected in either the water-deprivation or the limited access designs, although mean ethanol preference ratio declines after NT in the LAP design due to a tendency toward increased water intake.

Our data is in accordance with many previous reports that demonstrate that feeding is significantly reduced by intracranial, intravenous, or intraperitoneal NT (3,18,20,21,23,24,32, 36,44,48-50). Also, it has been shown before that water intake

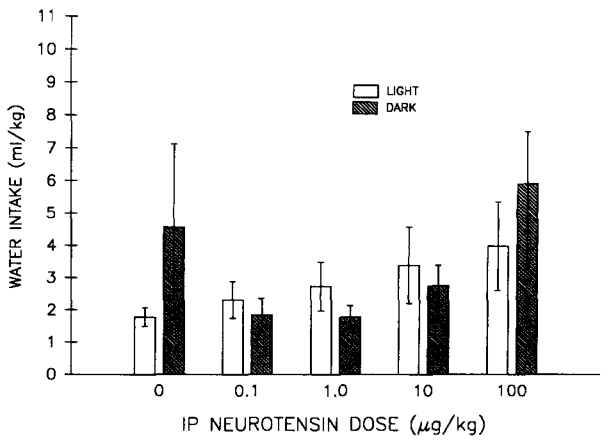

FIG. 8. Mean (±SE) water intake (ml/kg) of rats as a function of IP dose of NT during light or dark phase of the lighting cycle in LAP.

increases with ICV or IV neurotensin (2,22,48). Grooming behavior has repeatedly been shown to decrease after ICV NT (10,29,52–57,59). In our designs, we did not observe a suppression of locomotion as previously shown when NT is injected centrally (9,15,25,26,41,42,46,58). Since only very low basal levels of locomotion were recorded in our paradigms, a floor effect of this variable likely prevented detection of such an effect of NT on locomotion. Our data extend the above-described findings on the behavioral actions of neurotensin to the case of NT injected intraperitoneally rather than centrally or intravenously.

Feeding was reduced only in the later (i.e., 10–30 min after injection) stages of intake, and this is in accordance with criteria for a true "satiety" effect of a peptide on feeding (1,4,31). Simple debilitation or sedation could not have caused the decreased feeding because water intake was increased and ethanol intake was unaffected while feeding declined. Further, no abnormal behaviors were seen, and a time course analysis revealed that a normal "behavioral sequence of satiety" is observed after NT-reduced feeding. Thus, NT could be regarded as a candidate neuropeptide satiety factor for feeding; however, relatively high intraperitoneal doses are needed. This may indicate that IP NT acts centrally if there is appreciable penetration of NT across the blood–brain barrier. Alternatively, circulating NT may affect the CNS via a weak point in this barrier, that is, a circumventricular organ such as the area postrema adjacent to the nucleus of the tractus solitarius [cf. (3,6)]. No effect on ethanol intake clearly indicates that NT is not a candidate satiety factor for the control of ethanol intake, and NT's inhibitory effect on ingestion is specific to source of calories. NT increases in rat plasma after food intake or alcohol intake (14,17), making more likely the idea that food consumption causes peripheral release of NT, which then acts as a rapid signal of satiety at peripheral and possibly central receptors to control food intake and satiety-associated behaviors.

Likewise, decreased grooming after IP NT is in accord with all previous reports of NT given centrally, and these actions were the most potent effects of IP NT we observed. The increased resting effect of NT is compatible with the notion that NT is an endogenous neuroleptic (41) and possibly useful as a model in pharmacotherapeutics for control of resting-related disorders. We have also found that IP NT (1,100 μg/kg) increases resting behavior observed after IP ethanol (2 g/kg) in the rat (45). These findings are congruent with demonstrations that centrally administered NT enhances ethanol-induced motor impairment and sedation or sleep time (12,16, 34,35,37,40,51).

These effects point to a physiological role for endogenous gut and/or brain neurotensin in the regulation of vertebrate behavior. Particularly sensitive effects of IP NT in the rat were seen in categories of grooming, feeding, and resting. Our data provide evidence that NT may function as a regulatory peptide to control behaviors associated with ingestion of food and fluid. Perhaps manipulation of NT and its receptors could be considered in strategies for the treatment of feeding, grooming (pruritis), and resting (anxiety) disorders in humans.

To summarize, we found that peripherally administered NT controls several rat behaviors in a manner that suggests a physiological role for circulating NT in the regulation of specific behaviors.

ACKNOWLEDGEMENTS

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