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Vasoactive Intestinal Peptide: Behavioral Effects in the Rat and Hamster

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KULKOSKY, P. J., J. S. DOYLE, V. I. COOK, G. W. GLAZNER AND M. A. FODERARO. *Vasoactive intestinal peptide: Behavioral effects in the rat and hamster*. PHARMACOL BIOCHEM BEHAV **34**(2) 387–393, 1989.—The behavioral effects of intracerebroventricular (ICV) injection of the brain-gut peptide vasoactive intestinal peptide (VIP) were quantified with a behavioral sampling technique in home-caged, nondeprived, male and female albino rats and golden hamsters. ICV VIP sex-dependently decreased observed resting behavior during 1 hr after injections in both rats and hamsters at 0.1–10.0 μg. Grooming behavior was increased in hamsters, and rearing and standing behaviors were increased in rats, sex-dependently at VIP doses that decreased resting. Drinking behavior was suppressed in rats by VIP at 10.0 μg. Intraperitoneal (IP) VIP (100.0 μg/kg) increased 5% ethanol intake and decreased eating behavior in fluid-deprived male rats. The increase in ethanol intake produced by IP VIP was prevented by IP cholecystokinin octapeptide (CCK, 4.0 μg/kg). VIP potently controls resting and ingestive behaviors, suggesting a role for this neuropeptide, along with CCK, in the feedback regulation of rodent behavior.

Vasoactive intestinal peptide Cholecystokinin octapeptide Resting behavior Ingestive behavior Rat Hamster

A basic octacosapeptide extracted from porcine lung and isolated from intestine was named vasoactive intestinal peptide (VIP) because of its potent systemic vasodepressor properties (38). Subsequent discovery of VIP and its receptors in high concentrations in mammalian nervous system led to the identification of this brain-gut peptide as a candidate neurotransmitter or neuromodulator (8, 30, 32). A compendious literature documents the neurobiological actions of VIP, but there are fewer studies of the behavioral effects of VIP administration (37). VIP is a candidate hypnogenic factor because central administration increases sleep accompanied by rapid eye movement (REM) in male and female cats and in male rats (6, 7, 21, 31, 34, 36), and application of a VIP antagonist decreases REM sleep in male rats (29). In contrast, intracerebroventricular (ICV) VIP activates spontaneous movement, including grooming behavior in male rats (14, 17, 18). Further, ICV VIP inhibits retention of a passive avoidance task and facilitates extinction of active avoidance behavior in male rats (4). Also in male rats, high doses of ICV VIP inhibit water intake induced by deprivation or ICV angiotensin II (15), and a low dose of ICV VIP reduces food intake slightly (41). Intrathecal administration of VIP produces analgesia by action on opioid and nonopioid pain mechanisms in female rats (20). Finally, systemic injection of a large dose of VIP reduces running wheel activity in male rats (33).

Thus, this neuropeptide has been studied as a long-term sleep factor, a short-term modulator of activity, and an acute inhibitor of learned avoidance, pain, and consummatory behaviors. In order to add to this knowledge, the purpose of the first experiment is to clarify empirically the short-term behavioral actions of centrally administered VIP, and further explore its species and sex specificities in home-caged male and female laboratory rats and hamsters. In a second experiment, the behavioral effects of intraperitoneally (IP) administered VIP are evaluated in a paradigm that optimizes the consummatory behaviors of water and ethanol intake and feeding in male rats. A recent hypothesis states that neuropeptides of the brain and gut function as regulatory feedback controls of ethanol intake and other ingestive behaviors (23). For example, a negative feedback control is suggested by the findings that intragastric ethanol administration stimulates secretion of cholecystokinin (CCK), a brain-gut peptide and hormone, in the rat (25), and peripheral injection of bioactive CCK in rats reduces ethanol intake and blood ethanol levels (22,24). Recent reports demonstrate that ethanol administration increases the secretion and alters the actions of VIP (3, 39, 40). Therefore, VIP could function as a regulatory peptide in the adaptive limitation or stimulation of ethanol consumption and associated behaviors. Several studies indicate that VIP and CCK may function as antagonists in control of adrenocortical secretion and behavior (12–14, 17–19). Therefore, the ability of VIP and CCK to counteract reciprocal changes in ethanol intake is also tested. The results allow characterizations of the short-term effects of ICV VIP on rat and hamster home-cage behavior and the effects of IP VIP on deprivation-induced fluid intakes and associated behaviors in the rat.

METHOD

Animals

For studies of ICV VIP, ten experimentally-naive, adult golden

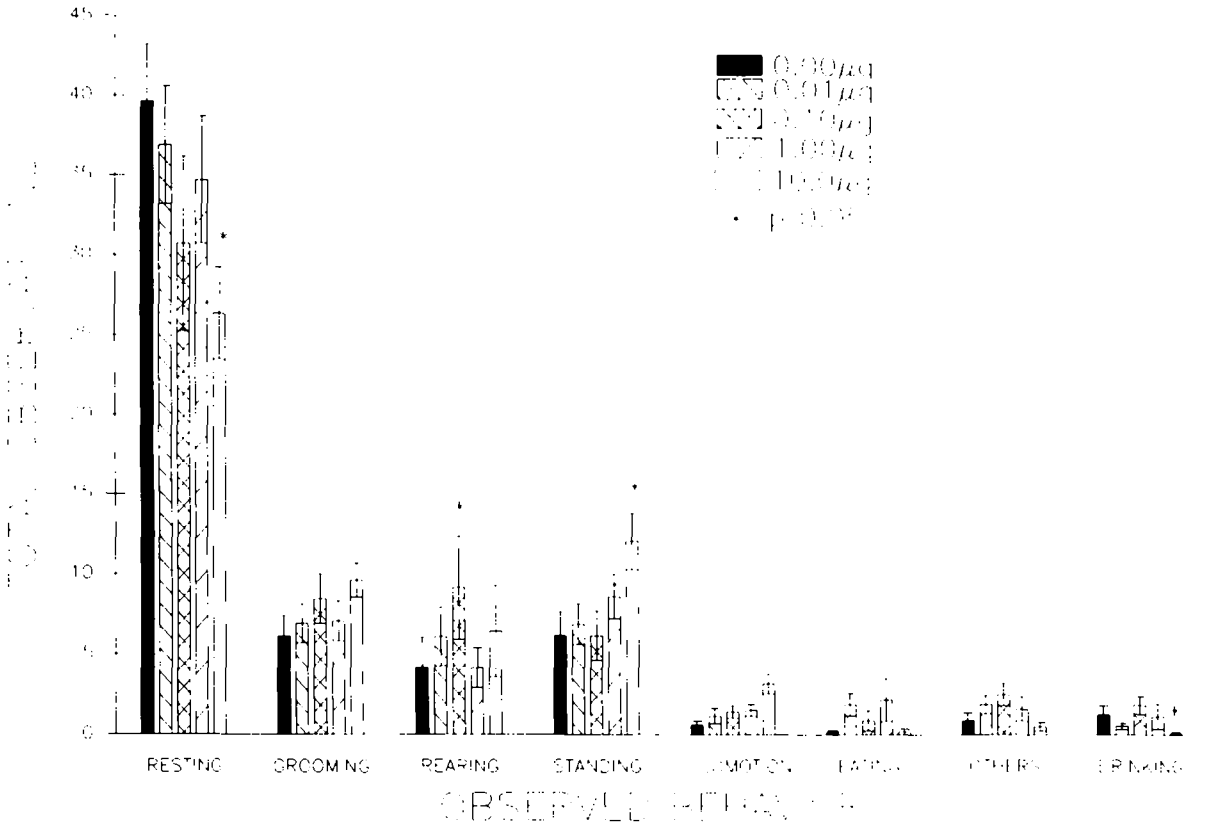

FIG. 1. Mean (± standard error, SE) total counts of observations of rats made in behavioral categories for 60 min after ICV injection of CSF or doses of VIP.

Syrian hamsters (*Mesocricetus auratus*) (outbred, Charles River, Inc., Wilmington, MA, Lak:LVG(SYR), 5 male, 5 female) were housed individually in circular plastic tubs (35.6 D × 22.2 H cm). Eleven experimentally-naive, adult Wistar Norway rats (*Rattus norvegicus*) (outbred, Charles River, Inc., Crl:(WI)BR, 6 male, 5 female) were housed individually in rectangular plastic cages (45.0 L × 23.5 W × 20.0 H cm) with wire metal lids. Twelve naive male Wistar rats were used in a second experiment on IP VIP. These animals were housed in wire-mesh home cages (24.0 L × 18.0 W × 18.0 H cm). All animals had ad lib access to food (Ralston Purina, Inc., St. Louis, MO, Rodent Laboratory Chow #5001) and deionized water. All plastic cages were lined with sawdust bedding and the hamsters were also given paper strips for nesting purposes. The animals were housed in an environment of approximately 23°C on a 12:12 L:D lighting cycle (0800 on) and tested between 0930 and 1330.

Surgery

All animals were anesthetized with sodium pentobarbital (40–80 mg/kg), IP after atropine sulfate pretreatment. A chronic stainless steel guide cannula (Plastic Products, Inc., Roanoke, VA, #C313G) was implanted via stereotaxic surgery in the left lateral ventricle of each animal. With skull in a level position, the tip of the guide cannula was positioned 2.2 mm beneath the dura, 1.1 mm anterior to bregma, and 1.7 mm lateral to the mid-sagittal suture for the hamsters, and was positioned 3.0 mm beneath the dura, 1.2 mm posterior to bregma and 1.5 mm lateral to the mid-sagittal suture for the rats. The tip of the injector cannula (Plastic Products, Inc., #C313I) extended 0.5 mm beyond the tip of the guide cannula. A dummy cannula (Plastic Products, Inc., #C313DC) was inserted into the guide cannula and left there between injections. Artificial cerebrospinal fluid (CSF) served as a vehicle for vasoactive intestinal peptide (porcine, Bachem, Inc., Torrance, CA) doses at concentrations of 0.01, 0.1, 1.0, and 10.0 μg/5 μl. All solutions were prepared freshly daily, administered over 10 sec in 5 μl volumes and delivered via microsyringe and polyethylene tubing while the animals were restrained by hand. Subsequently, ventricular placement of cannula tip was verified in each animal by methylene blue dye injection, sacrifice with sodium pentobarbital overdose, formalin perfusion and histological examination of 40 μm brain sections.

Procedure

Intracerebroventricular VIP. The following procedure was used to record the behavioral effects of ICV VIP in the home-caged, nondeprived rat and hamster: during the initial baseline adaptation phase of 3 days, the animals were removed from their cages and given an ICV injection of CSF alone (0.0 μg) and then replaced in the home cage. Immediately after being replaced in their cages, a 1-hour observation period began. Animals were observed at 0.6-sec tone-cued 1-minute intervals for a total of 60 observations. Their behaviors were classified and recorded as described previously (24). Seven specific categories of behaviors were recorded: grooming, resting, rearing, standing, locomotion, eating, and drinking. An eighth category was denoted as "others." This category contained all observed behaviors that were not classed in one of the other seven categories and included digging,

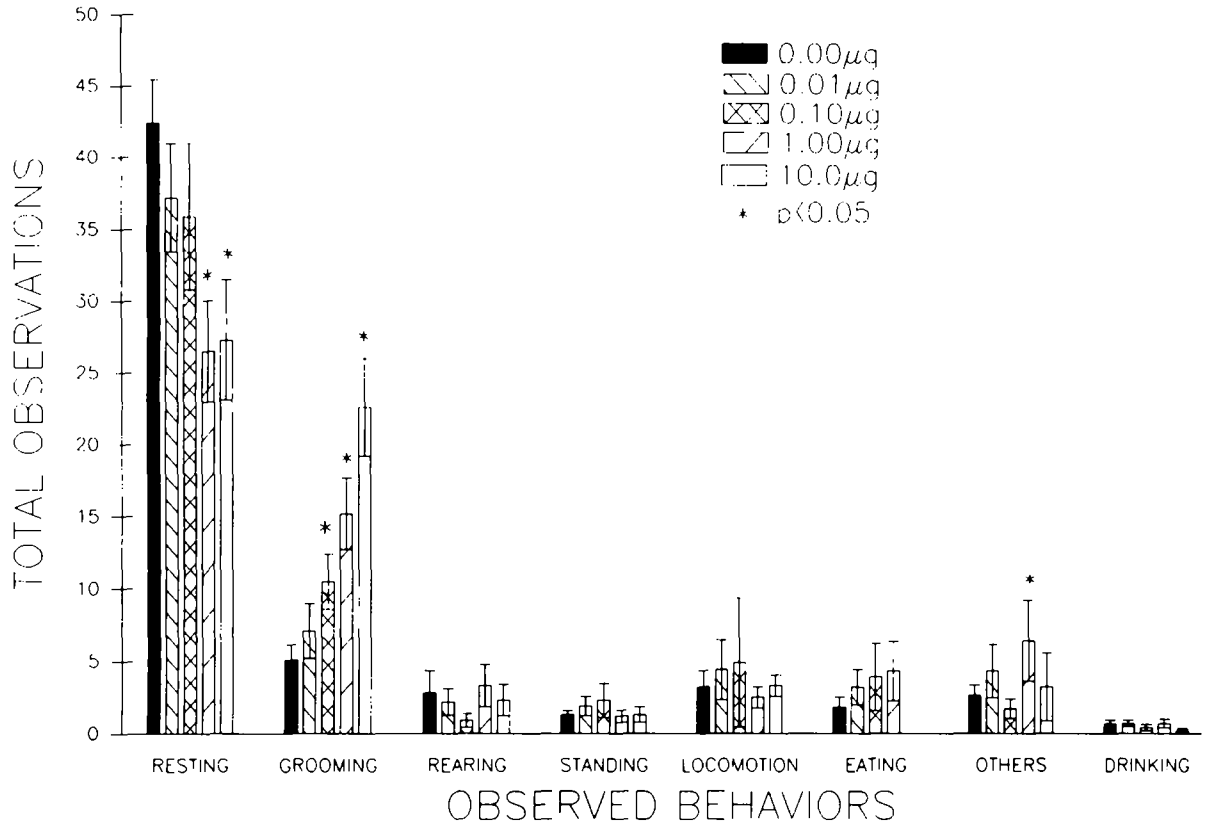

FIG. 2. Mean (±SE) total counts of observations of hamsters made in behavioral categories for 60 min after ICV injection of CSF or doses of VIP.

sniffing, jumping, and any other, unidentified behaviors. Following the adaptation phase animals were randomly assigned to receive either an ICV injection of CSF alone, or one of the 4 doses of VIP, on each of a total of 5 days of testing. Thus, each animal received an independently randomized sequence of VIP doses.

Intraperitoneal VIP. In the first phase of this experiment, all animals were deprived of water for 23 hours. The rats were given a 1.0 ml/kg intraperitoneal (IP) injection of saline (0.9% NaCl). Immediately after the injection, the animal was placed back into the cage. Six of the animals were randomly assigned to receive a 5% w/v ethanol solution for 45 min, and the other six were given deionized water. After the 45 min, the bottles were removed and then measured, and a bottle of deionized water was replaced for a 15-min period. From the time of injection, all animals were observed for 45 minutes with the behavioral observation method described above. Following this adaptation procedure, the rats were randomly assigned each day to receive an IP injection of either 0.0 (saline), 0.1, 1.0, 10.0, or 100.0 μg/kg of VIP in a 1.0 ml/kg volume. The experiment continued for 5 days, with each animal receiving a different dose each day, as described above.

In the second phase of this experiment, the animals were deprived and maintained as described above. Each rat received an IP injection of saline, then was placed back into the home cage and given a bottle of 5% w/v ethanol. The ethanol solution remained on the cage for 30 min, then the bottle was removed, and measured, and a bottle of deionized water was replaced for 30 min. After an adaptation period of 3 days, the 12 animals were randomly assigned to receive a 1 ml/kg intraperitoneal injection of either 0.0 (saline), 4.0 μg/kg of CCK (sulfated octapeptide, Squibb, Inc., Princeton, NJ, SQ 19,844), 100.0 μg/kg of VIP, or 4.0 μg/kg of CCK and 100.0 μg/kg of VIP. This procedure was continued for four consecutive days, until each rat had received each dosage treatment.

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

RESULTS

Intracerebroventricular VIP

Mean (±standard error, SE) total observations recorded in categories of behavior after ICV VIP doses is shown in Fig. 1 and 2 for rats and hamsters respectively. Dose of ICV VIP had significant ($p<0.05$) main effects on the categories of resting, grooming, eating, and drinking, respective, $F(4,68)s = 6.19, 17.62, 3.45, 2.63$. Significant main effects of species (rats vs. hamsters) were detected in the categories of grooming, standing and rearing, respective, $F(1,17)s = 9.86, 42.67, 5.01$. A significant main effect of sex was found only in the category of grooming, $F(1,17) = 8.16$. Interactions of VIP dose and species were significant in the categories of grooming and standing, respective, $F(4,68)s = 8.86$ and 3.43. Interactions of VIP dose and sex were significant in the categories of grooming and rearing, respective, $F(4,68)s = 4.27$ and 3.37. Interactions of VIP dose, species, and sex were significant in the categories of grooming and resting, respective, $F(4,68)s = 2.51$ and 2.95. Grooming behaviors were observed more frequently in hamsters, and were increased significantly by

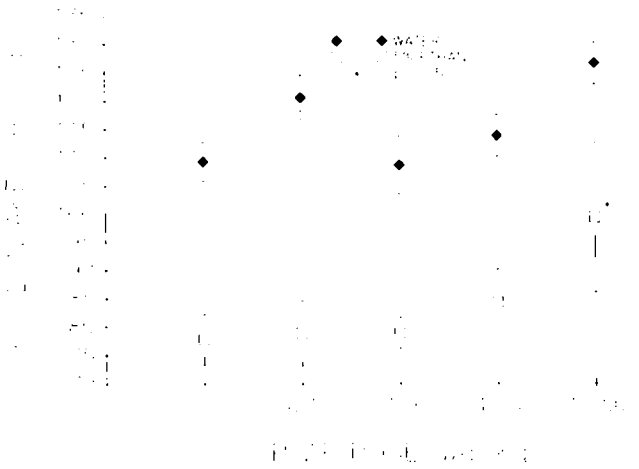

FIG. 3. Mean (±SE) fluid intake of fluid-deprived rats receiving either water or 5% w/v ethanol in a 45-min session after IP injection of saline or doses of VIP.

ICV VIP doses of 0.1–10.0 μg in male hamsters and 1.0–10 μg in female hamsters only. Standing behaviors were more frequently observed in rats, and were significantly elevated by an ICV VIP dose of 10.0 μg, in rats only. Rearing behaviors were observed more often in rats, and were significantly increased by 0.1 and 10.0 μg of VIP in female and male rats, respectively. Mean observed drinking behavior was significantly decreased at 10 μg of VIP in rats. Inspection of means revealed that "other" behaviors of digging, nesting and climbing were significantly increased in hamsters only, at 1.0 μg of VIP. Decreases in resting were significant at 10.0 μg in male rats and female hamsters, and at 0.1–10.0 μg of VIP in male hamsters. A time-course analysis of the effect of ICV VIP on resting behaviors revealed that in rats (N = 11), ICV VIP decreased resting behaviors at 45–50 min at 0.1 μg, and at 15–20, 25–30, and 40–50 min at 10.0 μg. In hamsters (N = 10), ICV VIP decreased observed resting at 50–55 min at 0.1 μg, at 20–50 min at 1.0 μg, and at 5–25 and 40–45 min at 10.0 μg. ICV VIP decreased resting behaviors in both rats and hamsters within an hour of injection. Nonresting behaviors increased after ICV VIP in a dose-, sex-, and species-dependent manner, as grooming behaviors were increased dose-dependently in male and female hamsters, but standing and rearing were increased dose-dependently in male and female rats at 0.1–10.0 μg. When data of both groups of rodents were combined, eating increased at 1.0 μg, and drinking decreased at 10.0 μg of VIP, although proportionally few ingestive behaviors were observed in these nondeprived, home-caged animals.

Intraperitoneal VIP

Phase 1. Figure 3 displays mean (±SE) intakes of water and 5% ethanol by fluid-deprived rats (Ns = 6) during a 45-min session, after doses of IP VIP. Statistical analysis revealed a significant effect of fluid type, $F(1,10) = 44.71$, as rats consumed more water than ethanol, and a significant effect of VIP dose,

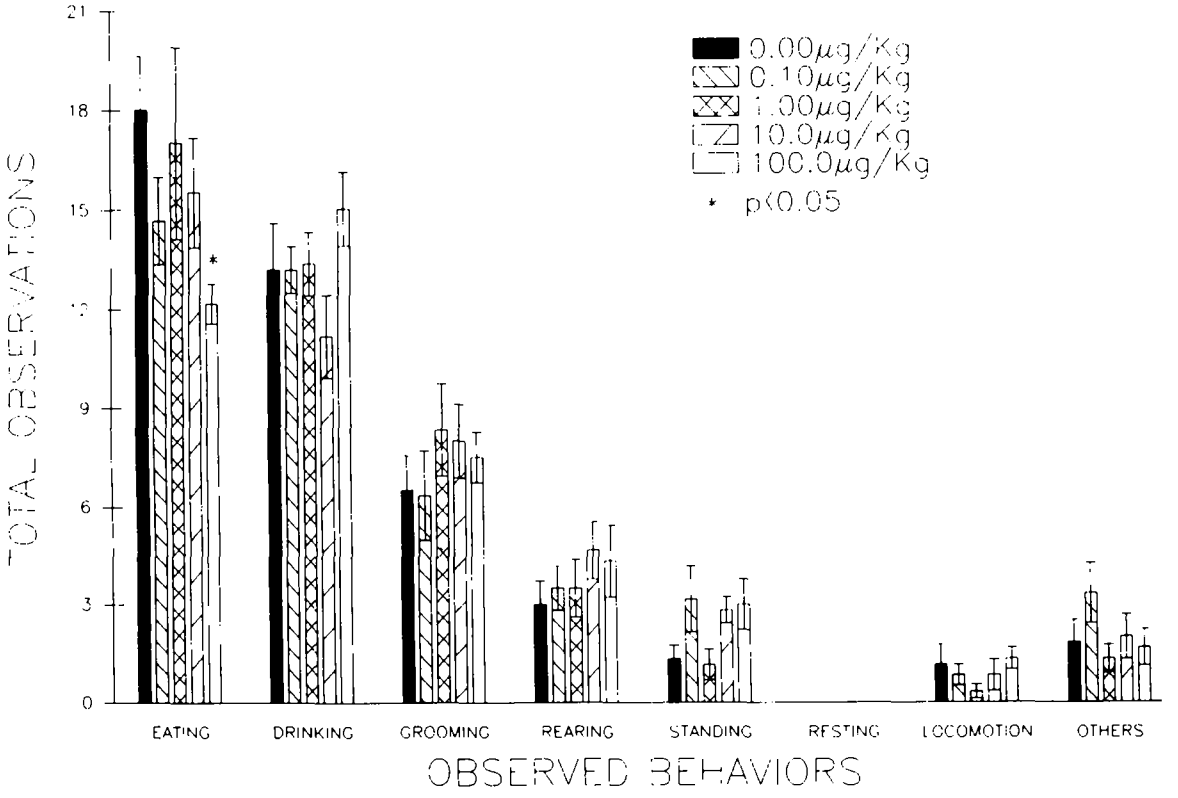

FIG. 4. Mean (±SE) total counts of observations made in behavioral categories for rats receiving water for 45 min after IP injection of saline or doses of VIP.

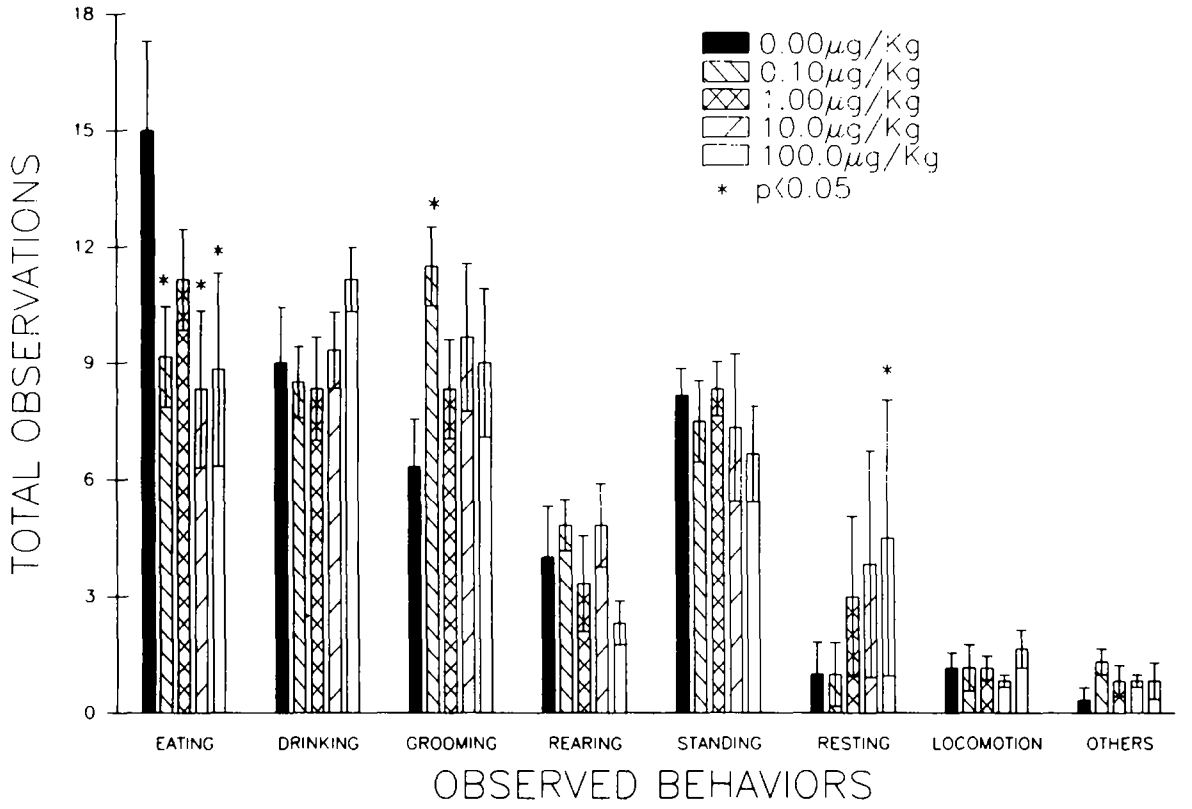

FIG. 5. Mean (±SE) total counts of observations made in behavioral categories for rats receiving 5% ethanol for 45 min after IP injection of saline or doses of VIP.

F(4,40) = 3.88. At a dose of 100 μg/kg, rats consumed more ethanol solution, relative to saline control. Mean (±SE) total observations recorded in categories of behavior after IP VIP doses is shown in Figs. 4 and 5 for rats receiving access to water or 5% ethanol, respectively. Dose of IP VIP had significant main effects on the categories of eating and drinking only, respective, F(4,40)s = 3.59 and 2.95. Significant main effects of fluid type (water vs. ethanol) were detected in the categories of eating, drinking, standing, and "other" behaviors, respective, F(1,10)s = 12.41, 12.37, 36.15, 6.85. Eating behavior was more frequent in the water-receiving group, and decreased significantly in the ethanol-receiving group at IP VIP doses of 0.1, 10.0, and 100.0 μg/kg, and in the water-receiving group at 100 μg/kg. Observed drinking behavior was more frequent in the water-receiving group, and increased in all rats (N = 12) at 100.0 μg/kg of VIP. Standing and "other" behaviors were more and less frequently observed, respectively, in the ethanol-receiving group. Increases in grooming and resting were noted in the ethanol-receiving group, at VIP doses of 0.1 and 100.0 μg/kg respectively.

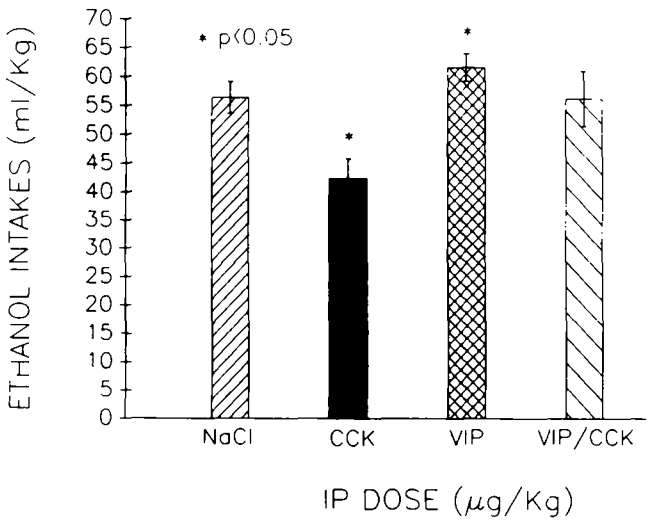

FIG. 6. Mean (±SE) 5% ethanol intake of rats for 30 min after IP injection of saline, CCK, VIP, and CCK+VIP.

Phase 2. Mean (±SE) 5% w/v ethanol intake by rats after 1 ml/kg IP injections of saline, 4.0 μg/kg CCK, 100.0 μg/kg VIP or CCK+VIP is shown in Fig. 6. Both CCK and VIP had significant main effects on ethanol intake, respective, F(1,11)s = 12.82 and 5.82. While CCK alone decreased ethanol intake and VIP alone increased ethanol intake, the combination of these doses of CCK and VIP had no effect on ethanol intake. Thus, CCK and VIP appeared to counteract reciprocal peptide-induced changes in ethanol intake.

DISCUSSION

Experimental data reveal potent, prompt behavioral effects of central and peripheral administrations of vasoactive intestinal peptide. The specific behavioral categories affected, and the direction of VIP effects depend on the dose, species, sex, deprivation status, and site of administration of the peptide. The

most reliable behavioral effect of ICV VIP in the home-caged rodent was the short-term inhibition of resting behavior, which was observed in both rats and hamsters at 0.1–10 μg. This finding accords with and extends previous reports of hypermotility or excitation immediately after ICV VIP in the rat (14,18). The acute inhibition of resting by central VIP appears to contrast with the literature of VIP as a peptide sleep-induction factor (6, 7, 21, 31, 34, 36). However, it has also been reported that ICV VIP significantly reduces pentobarbital-induced sleep in rats (14). It is possible that acute suppression of resting by VIP in the first hour after injection is followed by compensatory increases in sleep measured across the subsequent 23 hours, in an opponent-process regulation of resting. Stimulation of nonresting behaviors was dose-dependent, and species- and sex-specific, as grooming behaviors increased in male and female hamsters, and standing and rearing behaviors increased in male and female rats after doses of ICV VIP. An increase in grooming after 10 μg of ICV VIP was previously reported in the rat (17). ICV VIP potently stimulates prolactin and adrenocorticotropic hormone (ACTH) release (13, 16, 35), and prolactin and ACTH are both well known to induce excessive grooming behavior (5,11). Thus, grooming induction by ICV VIP could represent an indirect neuroendocrine action. ICV VIP nearly abolished drinking behaviors in rats at 10 μg, in accord with previous observations of antidipsogenic effects of centrally-injected VIP in rats (15).

Sex differences in the effects of ICV VIP were found in different thresholds of males and females for increases in grooming in hamsters, increases in rearing in rats, and decreases in resting in hamsters and rats. These differences are of interest because VIP is proposed as a central and peripheral regulatory peptide of the reproductive system (10). VIP is found prominently in the genito-urinary tract (10,32), and VIP levels in hypothalamus and pituitary are affected by estradiol levels (26,37).

Species differences in the effects of ICV VIP were found in grooming, which increased significantly only in hamsters, and in standing and rearing, which increased only in rats. Norway rats and golden hamsters are myomorph rodents of the murid and cricetid families, respectively. Murids are typically more active, versatile and speedier than comparable cricetids, and as a group, have larger brain:body ratios (27). This characterization seems reflected in the stimulation by VIP of self-maintenance behaviors in the hamster and exploratory and vigilance behaviors in the rat.

In sharp contrast with the results of central injection, peripheral injection of VIP significantly increased 5% ethanol intake and increased drinking behavior in fluid-deprived rats. Further contrasts of the effects of ICV and IP injection are seen in the categories of feeding, which only decreased after IP VIP, and resting, which increased slightly after IP VIP in rats drinking 5% ethanol. These results indicate that VIP selectively increases ethanol intake, because water intake was not significantly increased, and feeding was decreased (28). VIP could act endogenously and specifically to initiate, sustain or reinforce ethanol consumption. Research in gastroenterology has demonstrated that intravenous ethanol promptly and strongly stimulates release of radioimmunoactive VIP in humans (40). Further, intraduodenal ethanol, duodenal acidification, gastric vagus nerve or colonic pelvic nerve stimulation, mechanical stimulation of gut mucosa, and intragastric instillation of fat all elevate plasma VIP levels in mammals (1, 2, 9, 39). Taken together, behavioral and physiological results indicate that VIP could function as a regulatory peptide in the feedback control of ingestive behaviors, prominently including ethanol consumption. Alterations in VIP neurobiology may underlie, or be used to treat pathological variations in the control of alcoholism and feeding- and drinking-related disorders.

The stimulatory effect of IP VIP on ethanol intake can be counteracted by the inhibitory effect of IP CCK, and conversely, CCK's inhibition of ethanol intake can be abolished by IP VIP. These peptides thus appear to act as co-antagonists in the control of ethanol intake. Reciprocal antagonism of behavioral effects of VIP and CCK has been previously reported with respect to VIP-induced hypermotility, body shaking responses, and adrenocortical secretion (12, 14, 19). Present observations strengthen the suggestion that endogenous VIP and CCK could interact to control behavior integratively.

Vasoactive intestinal peptide potently alters behavioral displays in a dose-, species-, sex-, deprivation-, and site-specific manner. Central VIP administration reliably inhibits resting and elicits species-, sex- and dose-dependent increases and decreases in other behavioral categories. Peripheral VIP administration elevates ethanol intake in the rat, and inhibits feeding. The increase in ethanol intake after IP VIP can be antagonized by IP cholecystokinin administration, which suggests a potentially useful interaction of regulatory peptides in the control of alcohol consumption and associated behaviors. The potency and complexity of VIP's effects on behavior warrant further study in models of human disorders of ingestive and resting behaviors.

ACKNOWLEDGEMENTS

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