Pharmacology Biochemistry and Behavior, Vol. 58, No. 3, pp. 673–677, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00017-8

Decreased Intake of a Liquid Diet in Nonfood-Deprived Rats Following Intra-PVN Injections of GLP-1 (7–36) Amide

L. R. McMAHON AND P. J. WELLMAN[1]

Behavioral Neuroscience Program, Department of Psychology, Texas A&M University, College Station, TX 77843-4235

Received 4 August 1996; Revised 12 December 1996; Accepted 24 January 1997

McMAHON, L. R. AND P. J. WELLMAN. *Decreased intake of a liquid diet in nonfood-deprived rats following intra-PVN injections of GLP-1 (7–36) amide.* PHARMACOL BIOCHEM BEHAV **58**(3) 673–677, 1997.—ICV administration of glucagon-like peptide-1 (7–36) amide (GLP-1) dose dependently suppresses food intake in rats, and induces activation of c-*fos* within rat paraventricular hypothalamus (PVN). The present study sought to determine whether GLP-1 (7–36) amide may act within the PVN by examining the effects of intra-PVN administration of GLP-1 (7–36) amide on food intake in rats. Adult male rats ($n = 11$) were prepared with indwelling guide cannulae aimed at the PVN. Rats were allowed access to a palatable liquid diet (Ensure) and water during a daily 60-min test period with intakes measured every 15 min. Intra-PVN administration of GLP-1 (7–36) amide (10, 50, 100, and 200 ng) did not alter latency to feed, but did suppress liquid diet intake over a 1-h testing period, as a function of dose. These results suggest that GLP-1 (7–36) amide may act, in part, to suppress feeding through interactions with cells within the PVN. © 1997 Elsevier Science Inc.

Norepinephrine Paraventricular Nucleus Peptide Feeding

GLUCAGON-LIKE peptide-1 (7–36) amide (GLP-1) is secreted by the distal ileum following the ingestion of certain chemicals contained in foods. The functional significance of GLP-1 (7–36) amide in the digestive system includes the stimulation of glucose-dependent insulin secretion, and the inhibition of glucagon secretion as well as gastric emptying (13,23).

GLP-1 (7–36) amide may play a role in the central modulation of feeding (12,13,21). Turton et al. (21) noted that intracerebroventricular (ICV) administration of GLP-1 (7–36) amide reduced food intake in fasted rats at doses of 10–100 μg. In contrast, systemically administered GLP-1 (7–36) amide did not alter food intake, suggesting that GLP-1 (7–36) amide acts centrally and not peripherally to inhibit feeding. Anorexia has also been noted by other investigators using infusion of GLP-1 (7–36) amide into lateral ventricle (19), third ventricle (12,20), and fourth ventricle (11).

Using the induction of c-*fos* as a marker for neuronal activation, ICV administration of GLP-1 (7–36) amide resulted in cellular activation in the paraventricular nucleus of the hypothalamus (PVN) (20,21). Several additional lines of evidence suggest the PVN as a possible site of action for the inhibitory effect on feeding following central injections of GLP-1 (7–36) amide. The hypothalamus has been determined to exhibit a high concentration of GLP-1 (7–36) amide-like immunoreactivity as well as a high density of binding sites for GLP-1 (7–36) amide, the latter finding including the PVN (6,7,21). The hypothalamus has also been determined to release GLP-1 (7–36) amide in a calcium-dependent manner by potassium-induced depolarization, suggesting that GLP-1 (7–36) amide is a neurotransmitter within the hypothalamus (7). Moreover, Shughrue et al. (16) noted a dense accumulation of GLP-1 receptor mRNA within the rat PVN.

The PVN is an important central site in the control of feeding (3,8,9,26). Infusions of neurochemicals such as norepinephrine or NPY into the PVN dose dependently increase food intake (10,18). Conversely, infusions of serotonin into

[1]To whom requests for reprints should be addressed.

the PVN dose dependently decrease food intake (4,24). Given the established role of the PVN in the modulation of food intake, the expression of c-*fos* within the PVN following ICV infusions of GLP-1 (7–36) amide, and the high-density of GLP-1 (7–36) amide binding sites in the PVN, it is reasonable to hypothesize that the PVN may be a critical site of action for the suppression of feeding produced by ICV administration of GLP-1 (7–36) amide. The aim of the present study was therefore to examine the impact on food intake in rats of acute microinjections of doses of GLP-1 (7–36) amide (0, 10, 50, 100, and 200 ng) into the PVN.

METHOD

Subjects

The subjects were 14 adult male Sprague–Dawley albino rats (Harlan Industries, Houston, TX) weighing between 250–300 g at the beginning of the study. The animals were housed individually in standard plastic rodent cages and were allowed a 1-week adaptation period prior to the onset of behavioral testing to acclimate them to daily handling and colony maintenance procedures. The animal holding room was maintained at 23 ± 1.0°C, with a 12 L:12 D lighting schedule (lights on at 0600 h).

Diets

The rats received continuous access to rodent pellet-chow (Teklad) throughout the experiment except during the daily testing procedure when the rats were allowed access to a palatable liquid diet (Vanilla Ensure: 4% fat, 15% carbohydrate, 4% protein, 1.055 kcal/ml). The rats were allowed continuous access to tap water throughout the experiment including testing procedures.

Drugs

A norepinephrine solution (25 nmol) was prepared by dissolving ±arterenol hydrochloride (Sigma: A-0937) into Ringer's solution (composed of 145.0 mM NaCl, 2.7 mM KCl, 1.0 $MgCl_2 \cdot 6H_2O$, 1.2 mM $CaCl_2 \cdot 2H_2O$, and 2.0 mM Na_2HPO_4). The glucagon-like peptide-1 solutions (10, 50, 100, and 200 ng) were prepared by dissolving glucagon-like peptide-1, fragment 7–36, amide (Sigma: Lot #105H09201) into Ringer's solution. All solutions were calculated as the weight of the base molecule in 0.5 μl of Ringer's solution.

Surgical Procedure

Prior to surgery, each rat was injected (IP) with 0.4 mg/kg atropine sulfate (to minimize bronchial secretions), and then anesthetized using separate injections (5 min apart) of ketamine (Ketaset: 60 mg/kg, IP) and sodium pentobarbital (20 mg/kg, IP). With the upper incisor bar of the stereotaxic instrument positioned at 3.0 mm below the interaural line, the tip of each stainless steel guide cannula was positioned 1.6 mm caudal to bregma, 0.2 mm lateral to the midline, and 7.2 mm below the surface of the skull. The shaft of each guide cannula was affixed to the skull with stainless steel screws and a pedestal of dental acrylic. Following surgery, each rat received an injection (IM) of penicillin (300,000 units). A 7-day recovery period followed surgery, during which the rats were weighed daily and had continuous access to water and food pellets in the home cage.

Testing Procedure

The rats were trained to consume a palatable liquid diet (Vanilla Ensure) and tap water from separate metal sipper tubes attached to Wahmann 100 ml graduated drinking bottles during 60-min baseline test sessions. The sipper tubes were inserted through holes in the wire mesh ceiling above each cage. Fluid intakes were measured from the bottles to the nearest 0.5 ml and recorded for each rat. Before surgery, each rat underwent a series of five baseline test sessions. Following recovery from surgery, the rats underwent a series of four baseline test sessions. Beginning each day at 1400 h, feeders and water bottles were removed from each cage. Each rat was weighed, handled, and transferred to a clean home cage. During the baseline testing procedures, each rat was allowed access for 60 min to a Wahmann tube containing the liquid diet and a Wahmann tube containing tap water. The latency in seconds to begin consumption of the liquid diet was recorded for each rat (maximum latency was established at 30 s). Fluid intakes were recorded every 15 min for a total of four recordings during the 60-min test sessions. Fluid spillage was minimal and fluid intakes were not corrected for spillage. Bottle position was alternated daily according to a left or right position above the cage to control for position preference. The rats were then allowed free access to food and water until the next ingestive trial.

During the drug trials, liquid diet and tap water intakes were measured as outlined above. During the first drug trial, a single intra-PVN injection of 25 nmol norepinephrine (NE) was given to each rat to determine the probable locus of the guide cannula. Prior studies have indicated that this dose of NE reliably increases feeding upon injection into the PVN (15,25). The microinjector needle was positioned within each guide cannula so as to extend 0.5 mm beyond the tip of the cannulae. A volume of 0.5 μl was injected over a 10-s period, and the injector was left in place for an additional 50 s to allow diffusion of the drug solution into the injection site. Five minutes later, each rat was given access to the liquid diet and tap water. Following the injections of NE during the first drug trial and for the remaining drug trials, the animals underwent two 60-min nondrug test sessions on separate days between each succeeding drug trial to minimize drug carry-over effects. Each rat then received a single intra-PVN injection of each of the doses of GLP-1 (7–36) amide (0, 10, 50, 100, and 200 ng). Following the GLP-1 (7–36) amide drug trials, the rats received another injection of 25 nmol NE.

Histological Analyses

At the conclusion of the experiment, each rat was overdosed with sodium pentobarbital (60 mg/kg, IP), and perfused through the heart with 0.9% saline followed by 10% formalin. Further fixation in 10% formalin proceeded for at least 72 h prior to sectioning each brain. Alternate 80 μm frozen sections were photographically enlarged (×7), and compared to the atlas plates from Paxinos and Watson (14) to verify cannula placements.

Statistical Analyses

The present experiment represents a repeated measures design. The within-group factors represent either NE DOSE (0 and 25 nmol NE before (NE1) and after (NE2) the GLP-1 (7–36) amide drug series) or GLP-1 (7–36) AMIDE DOSE (0, 10, 50, 100, and 200 ng). Separate one-way analyses of variance (ANOVA: SigmaStat) were computed for liquid diet in-

take (ml consumed) using the within-group factors of either NE DOSE or GLP-1 (7–36) AMIDE DOSE. Separate ANOVAs were computed for cumulative 1-h liquid diet intake as well as for the first 15 min of diet intake. Inspection of the liquid diet data during the last 45 min revealed minimal intakes. In addition, these data failed tests of normality, and were therefore not included in the final data analyses.

Separate one-way ANOVAs were computed for latency to feed using the within-group factors of NE DOSE and GLP-1 (7–36) AMIDE DOSE. The ANOVAs were supplemented using a post hoc Student–Newman–Keuls test. Differences are noted as statistically significant for probability values less than 0.05 for all analyses. The water intakes were negligible in the present experiment and were therefore not subjected to data analyses.

RESULTS

Histology

Rats that exhibited cannula placements within the medial parvicellular and anterior parvicellular aspects of the PVN following blind histological inspection were included in the final data analyses. Eleven rats were determined to exhibit the proper anterior–posterior, medial–lateral, dorsal–ventral coordinate placements within the PVN (Fig. 1). Three rats exhibited ventral and/or lateral coordinate placements, and their data were not analyzed.

Effects of Norepinephrine on Ingestive Behavior

Intra-PVN injections of 25 nmol NE, given before (NE1) and after (NE2) the GLP-1 (7–36) amide drug trials, were used as an additional histological criterion to determine proper PVN placement. Figure 2a (top panel) depicts liquid diet intake in separate 15-min blocks (TIME BLOCKS 1–4) and total liquid diet intake (TOTAL) following intra-PVN injections of 25 nmol norepinephrine (NE1 and NE2) and vehicle. The NE1 and NE2 conditions in the present study resulted in increases of liquid diet intake (from vehicle intakes) of 34 and 18%, respectively, for the cumulative 1-h period (TOTAL), and of 21 and 18%, respectively, for the first 15-min period (TIME BLOCK 1). The three subsequent 15-min periods (TIME BLOCKS 2–4) exhibited a mixed pattern of liquid diet intake.

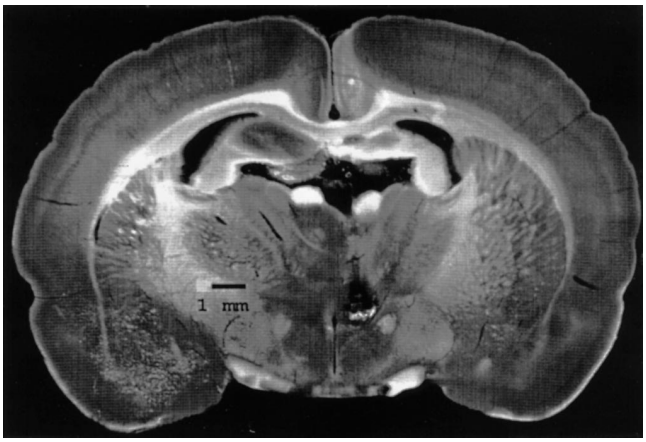

FIG. 1. Photomicrograph of a typical cannula placement within the PVN. The horizontal line represents 1 mm.

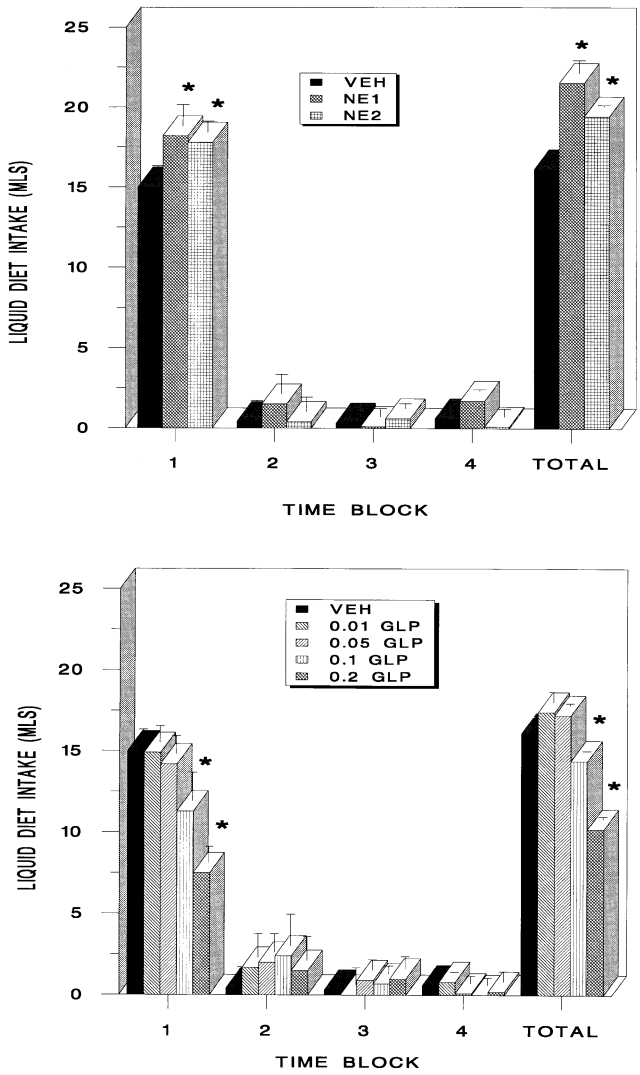

FIG. 2 (a) Mean group liquid diet intake (ml) recorded over four separate 15-min increments (TIME BLOCKS 1, 2, 3, and 4) and total liquid diet intake (TOTAL) following intra-PVN injection of either 25 nMol NE (before (NE1) and after (NE2) the GLP-1 (7–36) amide drug series) or vehicle (VEH). The vertical lines above each bar represent the standard error of the mean. Significant drug treatment differences relative to vehicle treatment are indicated by an asterisk ($*p < 0.05$). (b) Mean group liquid diet intake (ml) recorded over four separate 15-min increments (TIME BLOCKS 1, 2, 3, and 4) and total liquid diet intake (TOTAL) following intra-PVN injection of 0 (VEH), 10, 50, 100, and 200 ng GLP-1 (7–36) amide. The vertical lines above each bar represent the standard error of the mean. Significant drug treatment differences relative to vehicle treatment are indicated by an asterisk ($*p < 0.05$).

For cumulative 1-h liquid diet intake, a one-way repeated measures ANOVA revealed a significant effect of NE DOSE, $F(2, 32) = 9.97$, $p < 0.005$. A post hoc test using Student–Newman–Keuls procedure revealed that liquid diet intake during both the NE1 and NE2 treatments was significantly greater than vehicle intake during the cumulative 1-h period. For 15-min liquid diet intakes, a one-way repeated measures ANOVA revealed a significant effect of NE DOSE, $F(2, 32) = 5.05$, $p < 0.02$. A post hoc test using Student–Newman–Keuls

procedure revealed that liquid diet intake during both the NE1 and NE2 treatments was significantly greater than vehicle intake during the first 15-min period. A one-way repeated measures ANOVA revealed no significant differences in latency to consume the liquid diet between the NE1, NE2, and vehicle treatments, $F(2, 31) = 1.03$, $p > 0.38$.

Effects of GLP-1 (7-36) Amide on Ingestive Behavior

Figure 2b (bottom panel) depicts liquid diet intake in separate 15-min blocks (TIME BLOCKS 1–4) and total liquid diet intake (TOTAL) following intra-PVN injections of the doses of GLP-1 (7–36) amide (0, 10, 50, 100, and 200 ng). Intra-PVN injection of 10 and 50 ng GLP-1 (7–36) amide resulted in increases of liquid diet intake of 8 and 7%, respectively, for the cumulative 1-h period (TOTAL). Intra-PVN injection of 100 and 200 ng GLP-1 (7–36) amide resulted in decreases of liquid diet intake of 11 and 37%, respectively, for the cumulative 1-h period (TOTAL). Intra-PVN injection of GLP-1 (7–36) amide at doses of 10, 50, 100, and 200 ng resulted in decreases of liquid diet intake (from vehicle intakes) of 1, 6, 25, and 50%, respectively, for the first 15-min period (TIME BLOCK 1). The three subsequent 15-min periods (TIME BLOCKS 2–4) exhibited a mixed pattern of liquid diet intake.

For cumulative 1-h liquid diet intake, a one-way repeated measures ANOVA revealed a significant effect of GLP-1 (7–36) AMIDE DOSE, $F(4, 52) = 16.66$, $p < 0.005$. For 15-min liquid diet intakes, a one-way repeated measures ANOVA revealed a significant effect of GLP-1 (7–36) amide dose, $F(4, 53) = 11.21$, $p < 0.005$. A post hoc test using Student–Newman–Keuls procedure revealed that liquid diet intake following the 100 ng GLP-1 (7–36) amide dose was significantly different from intakes following vehicle and each of the other GLP-1 (7–36) amide doses (10, 50, and 200 ng) during the cumulative 1-h period and the first 15-min period. In addition, liquid diet intake following the 200 ng GLP-1 (7–36) amide dose was significantly different from intakes following vehicle and each of the other GLP-1 (7–36) amide doses (10, 50, and 100 ng) during the cumulative 1-h period and the first 15-min period. A one-way repeated measures ANOVA revealed no significant differences in latency to consume the liquid diet between the 0, 10, 50, 100, and 200 ng GLP-1 (7–36) amide treatments, $F(4, 53) = 0.22$, $p > 0.92$.

DISCUSSION

Intraventricular infusion of GLP-1 (7–36) amide into the rat results in a marked suppression of feeding (11,12,19, 20,21). The primary aim of the present study was to assess whether intra-PVN administration of GLP-1 (7–36) amide similarly reduces feeding in rats. In nonfood-deprived rats trained to consume a palatable, nutritive liquid diet, intra-PVN administration of GLP-1 (7–36) amide at doses of 100 and 200 ng decreased liquid diet intake during the cumulative 1-h period and the first 15-min period. GLP-1 (7–36) amide at doses of 10 and 50 ng had no significant effect on liquid diet intake at either time period. Moreover, no dose of GLP-1 (7–36) amide altered latency to eat. Thus, intra-PVN administration of GLP-1 (7–36) amide significantly reduced liquid diet intake without a concomitant change in latency to feed. The present results suggest that the anorexic effect of GLP-1 (7–36) amide is not peculiar to a food-deprived testing model, but can be observed in rats offered a palatable liquid diet. Because rats in the present study drank little water, whether GLP-1 (7–36) action within the PVN is specific to feeding cannot be determined. Others have noted that ICV GLP-1 reduces water intake, suggesting that this peptide may not have a specific action on feeding (19).

These results suggest that ICV administration of GLP-1 may act via activation of GLP-1 receptors within the PVN. Infusion of GLP-1 (7–36) amide into the lateral ventricles activates c-*fos* within a variety of nuclei in brain, including PVN, central nucleus of the amygdala (NUC AMYG), and anterior thalamic nucleus (21). Immunostaining studies reveal a high concentration of GLP-1 (7–36) amide in nerve cells within hypothalamus and low concentrations within midbrain, pons, and medulla (5,7). In contrast, autoradiography studies reveal high levels of GLP-1 (7–36) amide binding within the PVN, NUC AMYG, and anterodorsal thalamus, intermediate levels of binding within midbrain, pons, and medulla, and low levels of binding within cortex and cerebellum (6,21). Medial hypothalamic neurons express GLP-1 (7–36) amide receptors as well as proteins critical for sensing glucose (1), suggesting a putative linkage between glucose dynamics and modulation of feeding via GLP-1 (7–36) amide within the PVN. When considered together, these studies point to the PVN as being a focal point of GLP-1 (7–36) amide activity within brain. Whether GLP-1 (7-36) amide may also act to reduce feeding at nonPVN brain sites awaits further microinjection studies.

The finding that intra-PVN infusion of GLP-1 (7–36) amide reduces feeding in rats may shed light on a possible site of action for this peptide on feeding, but does not address whether GLP-1 (7–36) amide induces an early onset of "satiety" (17) or merely induces malaise, which in turn reduces food intake. Partial support for a satiety notion is apparent in the present study in that GLP-1 (7–36) amide did not alter latency to feed but did reduce overall intake. Further support for a satiety view of GLP-1 anorexic activity is derived from the recent report of Asarian et al. (2), who noted that ICV GLP-1 (7–36) amide suppressed sham-feeding and induced resting in the absence of grossly abnormal behaviors. Further behavioral assays of GLP-1 (7–36) amide activity in brain are required to determine whether GLP-1 induces satiety.

An alternate explanation for the present findings is that GLP-1 (7–36) amide induces malaise and subsequently reduces feeding. Such a view may be consistent with the action of GLP-1 on both food and water intake. Tang-Christensen et al. (19) noted that ICV infusions of 1 μg GLP-1 (7–36) amide suppressed feeding by 52% and reduced drinking by nearly 60% in rats. Although systemic injection of lithium chloride readily induced conditioned taste aversion (CTA), ICV administration of 1 μg GLP-1 (7–36) amide did not support conditioned taste aversion. Further dose–response analyses comparing anorexia and CTA are warranted to assess whether malaise may play a role in the anorexic property of GLP-1 (7–36) amide, specifically for administration of this peptide into the PVN. Another approach to assess the malaise hypothesis is to examine whether antagonism of the GLP-1 receptor results in increased feeding. Intra-PVN administration of the GLP-1 receptor antagonist exendin (9–39) increases feeding in satiated rats (22). The latter finding suggests that activation of GLP-1 receptors within the PVN may represent an effect on feeding that is independent of potential malaise effects of this peptide.

ACKNOWLEDGEMENTS

The authors thank Thompson Medical Company for support of this project. Portions of this manuscript were presented at the annual meeting of the Society for Neuroscience, Washington, DC, 1996.

REFERENCES

1. Alvarez, E.; Roncero, I.; Chowen, J. A.; Thorens, B.; Blazquez, E.: Expression of the glucagon-like peptide-1 receptor gene in rat brain. J. Neurochem. 66:920–927; 1996.
2. Asarian, L.; Cuomo, A. M.; Corp, E.; Hrupka, B.; Geary, N.: Glucagon-like peptide-1 (7–36 amide) elicits behavioral satiety in sham feeding rats. Soc. Neurosci. Abstr. 22:16; 1996.
3. Cooper, S. J.: Drugs and hormones: Their effects on ingestion. In: Toates, F. M.; Rowland, N. E., eds. Feeding and drinking, vol. 1. New York: Elsevier Science Publishers B.A.; 1987:231–269.
4. Fletcher, P. J.; Patterson, I. A.: A comparison of the effects of tryptamine and 5-hydroxytryptamine on feeding following injection into the paraventricular nucleus of the hypothalamus. Pharmacol. Biochem. Behav. 32:907–911; 1989.
5. Jin, S. L.; Han, V. K. M.; Simmons, J. G.; Towle, A. C.; Lauder, J. M.; Lund, P. K.: Distribution of glucagon like peptide 1 (GLP-1), glucagon, and glicentin, in the rat brain: An immunocytochemical study. J. Comp. Neurol. 271:519–532; 1988.
6. Kanse, S. M.; Kreymann, B.; Ghatei, M. A.; Bloom, S. R.: Identification and characterization of glucagon-like peptide-1 7-36 amide-binding sites in the rat brain and lung. FEBS Lett. 241:209–212; 1988.
7. Kreymann, B.; Ghatei, M. A.; Burnet, P.; Williams, G.; Kanse, S.; Diani, A. R.; Bloom, S. R.: Characterization of glucagon-like peptide-1-(7–36) amide in the hypothalamus. Brain Res. 502:325–331; 1989.
8. Leibowitz, S. F.: Paraventricular nucleus: A primary site mediating adrenergic stimulation of feeding and drinking. Pharmacol. Biochem. Behav. 8:163–175; 1978.
9. Leibowitz, S. F.: Hypothalamic paraventricular nucleus: Interaction between α2-noredrenergic system and circulating hormones and nutrients in relation to energy balance. Neurosci. Biobehav. Rev. 12:101–109; 1988.
10. Leibowitz, S. F.; Myers, R. D.: The neurochemistry of ingestion: Chemical stimulation of the brain and in vivo measurement of transmitter release. In: Toates, F. M.; Rowland, N. E., eds. Feeding and drinking, vol. 1. New York: Elsevier Science Publishers B.A.; 1987:271–315.
11. Moran, T. H.; Wohn, A.; Schwartz, G. J.; Ladenheim, E. E.: Fourth ventricular administration of glucagon-like peptide-1 (7–36) amide (GLP-1) inhibits food intake in rats. Soc. Neurosci. Abstr. 22:15; 1996.
12. Navarro, M.; Rodriguez de Foncesa, F.; Zueco, J. A.; Gomez, R.; Blazquez, E.: Changes in food intake induced by GLP-1 (7–36) amide in the rat. 15th International Diabetes Federation Congress, Kobe, Japan; 1994.
13. Orskov, C.: Glucagon-like peptide-1, a new hormone of the entero-insular axis. Diabetologia. 35:701–711; 1992.
14. Paxinos, G.; Watson, C.: The rat brain in stereotaxic coordinates, 2nd ed. New York: Academic Press; 1986.
15. Roland, C. R.; Oppenheimer, R. L.; Chang, K.; Leibowitz, S. F.: Hypophysectomy disturbs the noradrenergic feeding system of the paraventricular nucleus. Psychoneuroendocrinology 10:109–120; 1985.
16. Shughrue, P. J.; Lane, M. V.; Merchenthaler, I.: The distribution of glucagon-like peptide-1 receptor (GLP1-R) mRNA in the rat brain. Endocrinology 137:5159–5162; 1996.
17. Smith, G. P.; Gibbs, J.: Postprandial satiety. In: Sprague, J. M.; Epstein, A. N., eds. Progress in psychobiology and physiological psychology, vol. 8. New York: Academic Press; 1979:179–242.
18. Stanley, B. G.: Neuropeptide Y in multiple hypothalamic sites controls eating behavior, endocrine, and autonomic systems for body energy balance. In: Colmers, W. F.; Wahlestedt, C., eds. The biology of neuropeptide Y and related peptides. Totowa, NJ: Humana Press; 1993:457–509.
19. Tang-Christensen, M.; Larsen, P. J.; Goke, R.; Fink-Jensen, A.; Jessop, D. S.; Moller, M.; Sheikh, S. P.: Central administration of GLP-1-(7–36) amide inhibits food and water intake in rats. Am. J. Physiol. 271:R848–R856; 1996.
20. Thiele, T. E.; Van Dijk, G.; Donahey, J. C. K.; Campfield, L. A.; Smith, F. J.; Bernstein, I. L.; Woods, S. C.; Seeley, R. J.: Central infusion of leptin (OB protein) and GLP-1-(7–36) amide differentially stimulate c-fos expression in rat brain. Soc. Neurosci. Abstr. 15:1411; 1996.
21. Turton, M. D.; O'Shea, D.; Gunn, I.; Beak, S. A.; Edwards, C. M. B.; Meeran, K.; Choi, S. J.; Taylor, G. M.; Heath, M. M.; Lambert, P. D.; Wilding, J. P. H.; Smith, D. M.; Ghatei, M. A.; Herbert, J.; Bloom, S. R.: A role for glucagon-like peptide-1 in the central regulation of feeding. Nature 379:69–72; 1996.
22. Turton, M. D.; Edwards, C. M. B.; Khatib, O.; Ghatei, M. A.; Bloom, S. R.: Blockade of glucagon-like peptide-1 (7–36) NH_2 in the paraventricular nucleus of the hypothalamus increases feeding. J. Endocrinol. (Suppl.) 148:P126; 1996.
23. Wang, Z.; Wang, R. M.; Owji, A. A.; Smith, D. M.; Ghatei, M. A.; Bloom, S. R.: Glucagon-like peptide-1 is a physiological incretin in rat. J. Clin. Invest. 95:417–421; 1995.
24. Weiss, G. F.; Papadokos, P.; Knudson, K.; Leibowitz, S. F.: Medial hypothalamic serotonin: effects on deprivation and norepinephrine-induced feeding. Pharmacol. Biochem. Behav. 25:1223–1230; 1986.
25. Wellman, P. J.; Davies, B. T.: Suppression of feeding induced by phenylephrine microinjections within the paraventricular hypothalamus in rats. Appetite 17:121–128; 1991.
26. Wellman, P. J.; Davies, B. T.; Morien, A.; McMahon, L. R.: Modulation of feeding by hypothalamic paraventricular nucleus α1- and α2-adrenergic receptors. Life Sci. 53:669–679; 1993.