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Suppression of Peptide YY-Induced Hyperphagia by Terbutaline

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HAGAN, M. M. AND D. E. MOSS. *Suppression of PYY-induced hyperphagia by terbutaline.* PHARMACOL BIOCHEM BEHAV **46**(3) 679–681, 1993.—Central administrations of neuropeptide Y and peptide YY (PYY) produce robust increases in food intake, and this response may be contingent upon the availability of insulin. In contrast, β_2-adrenergic agonists decrease food intake, and this effect also appears to be dependent on circulating insulin. To investigate a possible interaction between PYY and β_2-adrenergic function, rats were given systemic injections of terbutaline, a β_2 agonist, at doses of 0, 5, 10, and 50 mg/kg prior to injections of 0.57 nmol PYY in the paraventricular nucleus of the hypothalamus. Terbutaline pretreatment significantly decreased feeding elicited by PYY in a dose-dependent fashion. This suggests that β_2-adrenoreceptor activity is involved in PYY-induced feeding.

Peptide YY Ingestive behavior Terbutaline β_2 adrenergic Hyperphagia Bulimia nervosa

PEPTIDE YY (PYY), a 36-amino acid peptide (17), produces exaggerated eating in satiated rats after intrahypothalamic and intracerebroventricular injection (4,11,15). Hyperpaghia induced by PYY and related neuropeptide Y (NPY) is suppressed by naloxone (6,10) and peripherally administered fluoxetine (6). In contrast, phentolamine (15), and the opioid-like Pro-Leu-Gly amide peptides, MIF-1 and Tyr-MIF-1 (unpublished data), have no effect in suppressing NPY- and PYY-induced eating, respectively.

The actions of naloxone, MIF-1, and Tyr-MIF-1 indicate that PYY and NPY may involve 5-HT and opioid mechanisms that are specifically naloxone sensitive. The results obtained with phentolamine suggest that NPY-induced hyperphagia does not require noradrenergic activity.

Besides the known anorexic properties of opioid blockers and 5-HT potentiating agents, β_2 adrenergics have also been shown to suppress spontaneous ingestive behavior (3,9). To further explore the role of possible β_2-adrenergic function in the regulation of PYY-induced hyperphagia, we examine the effect of peripherally administered terbutalin, a β_2-adrenoreceptor agonist, on animals whose intake was stimulated by PYY injection into the paraventricular nucleus of the hypothalamus (PVN).

METHOD

Subjects and Surgery

Female Sprague-Dawley rats, weighing 280–360 g at the time of the experiments and kept under standard lighting conditions (12L : 12D, lights on 0700), had free access to standard rat chow and water. Animals were anesthetized with sodium pentobarbital (65 mg/kg), and chronically indwelling 12-mm cannulae were unilaterally aimed at the paraventricular nucleus (PVN) (12) −1.8 mm posterior and −0.4 mm lateral to bregma. Depth was 7.6 mm from the skull surface and upper incisor bar was 3.3 mm below the interaural line. Rats were allowed to recover from surgery for a minimum of 7 days and were maintained in group cages.

Drugs

Food intake was stimulated by PVN injection of 0.57 nmol/3 μl porcine synthetic PYY. Animals were pretreated with the following: intraperitoneal (IP) terbutaline hemisulfate (TERB) in doses of 5, 10, and 50 mg/kg, or saline diluent (VEH). All drugs were obtained from Sigma (St. Louis, MO).

Procedures

Eating tests began 3 h after light onset. Animals had free access to food and water until the experiments were performed, at which time preweighed Purina rat chow pellets were placed in individual testing cages after each rat received a pretreatment of TERB immediately followed by PYY in the PVN. The amount of food eaten was measured by subtracting leftover food and spillage from the given amount at 1, 2, and 4 h. Drug conditions were administered in a counterbalanced, repeated measures design with 3 days between test sessions.

At the conclusion of the experiment, all animals were anes-

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thetized with sodium pentobarbital and perfused intracardially with physiological saline followed with 10% formalin. Injection sites were determined by frozen section histology. On average, cannulae tracts terminated at or immediately ventral to the intended PVN site. Results are expressed as mean ± SEM 4-h cumulative food intake in grams. Data were analyzed by a one-way repeated measures analysis of variance (ANOVA) using paired comparisons with alpha levels corrected for multiple tests.

RESULTS

ANOVA revealed an overall significant effect of drug conditions on food intake, $F(5, 50) = 17.47$, $p < 0.001$. As shown in Fig. 1, post hoc comparisons showed a main effect of PYY on food intake, $t(10) = 6.70$, $p < 0.01$, with animals eating 9.2 ± 0.9 g after PYY compared to the control intake of 2.3 ± 0.4 g. TERB (5 mg/kg) suppressed spontaneous intake, $t(10) = 4.33$, $p < 0.01$, with animals consuming 0.6 ± 0.2 g. TERB dose on PYY-induced eating revealed a suppressing effect of 5.0 mg/kg TERB, $t(10) = 4.92$, $p < 0.01$, of 10.0 mg/kg TERB, $t(10) = 4.43$, $p < 0.01$, and of 50.0 mg/kg TERB, $t(10) = 4.03$, $p < 0.01$, with animals eating 6.2 ± 0.7 g, 4.6 ± 1.1 g, and 4.1 ± 1.3 g, respectively.

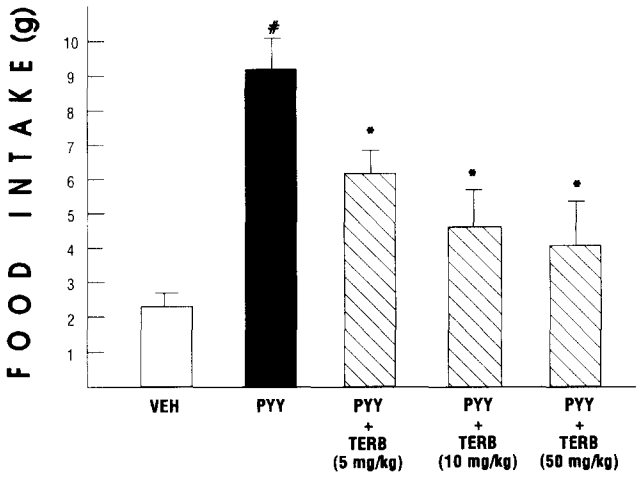

FIG. 1. The effect of various doses of IP TERB on 4-h food intake (mean ± SEM) produced by 0.57 nmol peptide YY (PYY) in the PVN. VEH = vehicle. #$p < 0.01$ different from VEH; *$p < 0.01$ different from PYY alone.

There was no difference in intake consumed by control animals and PYY-injected rats that were pretreated with the two higher doses of TERB. Pilot tests with a dose of 20 mg/kg TERB on PYY-induced intake revealed no significant differences between doses of 10.0 and 50.0 mg/kg TERB ($N = 7$, 4.1 ± 0.9 g mean intake) on PYY-induced hyperphagia.

DISCUSSION

The results of this study confirmed the potent hyperphagic actions of PYY injected into the PVN, as well as the anorexic properties of TERB as shown by suppression of spontaneous eating. More importantly, our results extend the previous research on PYY and show that the potent hyperphagic effect of PYY is suppressed by TERB. The most obvious implication is that the expression of PYY-induced feeding is inhibited by β_2-adrenergic activity.

A less obvious implication for these results is the possible central role of insulin in the mediation of these effects. Specifically, β_2 agonist-induced suppression of feeding requires circulating insulin. For example, Bitar et al. (1) showed that β_2 agonist suppression of feeding was impaired in diabetic rats but that suppression could be reestablished by pretreatment with insulin. Secondly, extrapolation of early results obtained with NPY to PYY suggests that insulin may be required for the expression of the effect of PYY on eating. In this experiment, PVN NPY-induced hyperphagia was abolished in diabetic rats (15).

However, there is also more recent evidence to suggest that NPY neurosecretion is increased in the PVN in association with streptozotocin-induced hyperphagia (14), and inhibition of NPY gene expression may be a mechanism by which hyperphagia results in the diabetic animal (18). Future research should determine whether or not there is a differential response to insulin availability and β_2 agonist activity between NPY- and PYY-induced feeding. The importance of studying these effects is suggested by clinical findings that show anorexic patients have anomalies in CSF NPY levels while bulimic patients show abnormal levels of CSF PYY (8), and that anorexic but not bulimic patients show reduced β_2 receptor capacity (13). If indeed there is a functional link between the neuropeptides and β_2 adrenoreceptors that is different for NPY and PYY, this difference would have valuable implications for understanding and treating eating disorders.

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