Hypothalamic α_2-Noradrenergic Receptor System

Relation to Dietary, Genetic, and Hormonally Induced Obesity

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Variables relating to diet, hormones, and genetic background are major factors in the development of obesity. Moreover, hypothalamic neurotransmitter systems are known to influence food intake, appetite, metabolism, and body weight. In particular, the catecholamine, norepinephrine (NE), has been shown in animals to potentiate food intake in satiated subjects, enhance appetite specifically for carbohydrate, affect circulating hormones and nutrients, and reduce energy expenditure.[1] This neurotransmitter, which produces hyperphagia and increased body weight gain with chronic administration, is found to act via α_2-noradrenergic receptors specifically in the hypothalamic paraventricular nucleus (PVN). Circulating substances, such as the glucocorticoid hormone corticosterone (CORT) and glucose, have been shown to influence these PVN α_2 receptors, as well as eating behavior.[2,3] Moreover, evidence suggests that this α_2-receptor system becomes most active and exerts its maximum physiological effects precisely at the start of active cycle, when circulating CORT levels normally peak and when eating behavior, and in particular carbohydrate preference, is strongest.[1-3]

This report reviews the results of three studies that have used radioligand receptor binding techniques to examine the α_2-noradrenergic receptors in discrete hypothalamic sites, including the PVN, of rats that are: (i) maintained for six weeks on a high-fat diet (Purina lab chow mixed with 30% wt/wt Crisco) versus lab chow; (ii) lean (FA/−) versus obese (fa/fa) genetically controlled animals of the Zucker strain; and (iii) adrenalectomized rats treated with either cholesterol or CORT or sham-operated rats treated with cholesterol.

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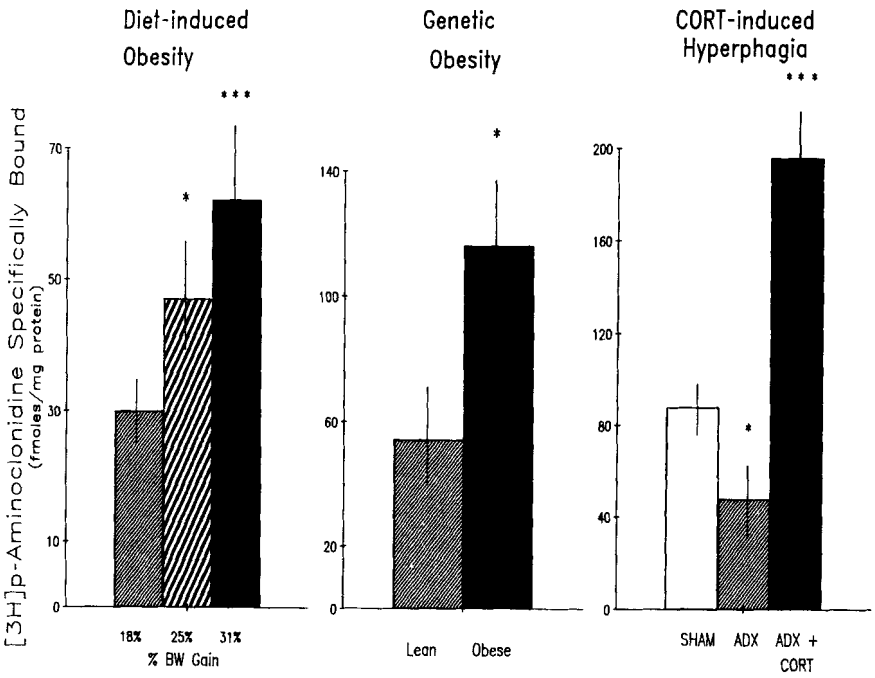

FIGURE 1. [^{3}H]*p*-aminoclonidine binding (fmoles/mg protein ± SEM) to α_2-noradrenergic receptors in the paraventricular nucleus (PVN) of rats that became moderate to severely obese when kept on high-fat diet (left panel), of lean and genetically controlled obese Zucker rats (middle panel), and of rats receiving either SHAM ADX + cholesterol implants (200 mg), ADX + cholesterol, or ADX + CORT (200 mg) (right panel). * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ for direct comparisons between groups.

METHODS

A standard radioligand binding technique, using the α_2-noradrenergic receptor agonist [^{3}H] *p*-aminoclonidine ([^{3}H]PAC; 45.8 Ci/mmol), was employed to determine the α_2-receptor density in seven micropunched hypothalamic areas. Nonspecific binding was determined in the presence of phentolamine, and the results are expressed as [^{3}H]PAC specifically bound in fmoles/mg protein.

RESULTS

Experiment 1: α^2 Receptors in Relation to Diet-Induced Obesity

The exposure to a high-fat diet for six weeks caused variable changes in body weight in individual rats, ranging from low to severe levels of obesity. Analyses of hypothalamic α_2 receptors (FIG. 1) indicated a significant increase in [^{3}H]PAC binding in the PVN of moderate (+50%; $p < 0.05$) and severely (+100%; $p < 0.001$) dietary-induced

obese rats, and also in the dorsomedial nucleus of severely obese rats, as compared to dietary-resistant and chow-fed rats (+100%; $p < 0.01$). In contrast, the density of α_2-noradrenergic receptors in other hypothalamic areas remained unchanged.[4]

Experiment 2: α_2-Noradrenergic Receptors in Genetically Controlled Obese and Lean Zucker Rats

FIGURE 1 presents the [^{3}]PAC binding results for the PVN of lean and obese Zucker rats. As shown here, genetically obese rats had a significantly greater number of available α_2-noradrenergic receptors in the PVN (+120%; $p < 0.05$) than did their lean littermates. Other hypothalamic areas, however, exhibited no group differences in their α_2-receptor density.

Experiment 3: α_2-Noradrenergic Receptors in Relation to Circulating Levels of CORT

As shown in FIGURE 1, the loss of circulating CORT through adrenalectomy (ADX) caused a significant decrement (−46%; $p < 0.05$) in [^{3}]PAC binding to α_2-noradrenergic receptors, specifically in the PVN.[2] Subcutaneous CORT implants, which raised circulating CORT levels to 14 μg%, totally and significantly reversed the [^{3}]PAC binding in the PVN ($p < 0.001$). This down regulation of PVN α_2 receptors in ADX rats, associated with a dramatic decline in eating behavior, was completely reversed by chronic subcutaneous CORT implants, which raised circulating hormone levels to 14 μg% and significantly increased food intake. The only other hypothalamic area affected was the supraoptic nucleus, which exhibited the opposite pattern of changes in α_2-receptor binding.

CONCLUSION

The results of these studies demonstrate that the α_2-noradrenergic receptors specifically in the PVN, which are known to have a role in the control of energy intake and expenditure, exhibit dramatic changes in relation to dietary, genetic, and hormonal factors that are known to contribute to the onset and maintenance of obesity. Further research is needed to establish whether these receptor changes precede or are consequent to the development of hyperphagia and weight gain.

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