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Higher α-Noradrenergic Receptors in Paraventricular Nucleus of Obese Zucker Rats: Decline After Food Deprivation

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JHANWAR-UNIYAL, M., I. R. AWAD, G. M. GEARHART, J. A. FINKELSTEIN AND S. F. LEIBOWITZ. *Higher α-noradrenergic receptors in paraventricular nucleus of obese Zucker rats: Decline after food deprivation.* PHARMACOL BIOCHEM BEHAV **40**(4) 853–859, 1991.—Norepinephrine (NE), acting through α_2-noradrenergic receptors in the hypothalamic paraventricular nucleus (PVN), has been implicated in the control of feeding behavior and body weight gain. To determine whether this hypothalamic receptor system is disturbed in genetically obese rats, the binding of radioligands to α_2-noradrenergic, as well as to α_1-noradrenergic, receptors was examined in seven hypothalamic nuclei of obese Zucker rats relative to their lean littermates. Receptor binding procedures, using the α_2-noradrenergic agonist [^{3}H]p-aminoclonidine ([^{3}H]PAC) and the α_1-noradrenergic antagonist [^{3}H]prazosin, demonstrated that the obese rats, compared to the lean rats, had significantly greater α_2-noradrenergic and α_1-noradrenergic receptor binding, specifically in the PVN as opposed to other hypothalamic areas examined. Moreover, the obese rats, compared to the lean rats, exhibited greater responsiveness to the effects of food deprivation (48 h), which caused a significant decline in radioligand binding to both α_2 and α_1 receptors, specifically in the PVN. A decrease in α_2-receptor binding after deprivation in the obese rats was also seen in two basal hypothalamic areas, namely, the supraoptic nucleus and arcuate nucleus-median eminence. The possibility exists that these disturbances in hypothalamic α-receptors may be involved in the development and/or maintenance of the genetic obesity.

Obesity Feeding behavior α-Noradrenergic receptors Norepinephrine Paraventricular nucleus Hypothalamus Zucker rats

THE syndrome of the genetically obese Zucker rat (fa/fa) is characterized by a variety of metabolic, endocrine and behavioral disturbances, seen relatively early in development. These include increased lipogenesis, hypothermia, hyperinsulinemia, low energy expenditure, increased activity of hypothalamo-pituitary-adrenal axis, and hyperphagia (5, 6, 40). The question, addressed by a number of investigators, is whether these physiological disturbances in the obese rat are related in any way to alterations in neurochemical systems of the brain. Studies conducted primarily in nonobese rats (31,32) have identified monoaminergic as well as peptide systems in the hypothalamus that have profound effects on food intake, hormone release, metabolism and body weight.

Measurements of brain catecholamines have shown that the female and male obese Zucker rats have reduced levels of norepinephrine (NE), specifically in the hypothalamic paraventricular nucleus (PVN) (8, 9, 38). This nucleus has been identified as the site of action for NE in the stimulation of food intake and body weight gain (31), as well as in the release of the adrenal hormone corticosterone (CORT) (36) and the reduction of energy expenditure (50). Moreover, electrolytic lesions of the PVN are found to produce hyperphagia and obesity (33, 49, 54). Thus the reduced levels of PVN NE detected in obese Zucker rats may be related to either a cause or consequence of the disturbances in feeding behavior, hypothalamo-pituitary-adrenal axis and metabolism exhibited by these animals.

The specific receptors mediating the action of NE in the stimulation of feeding behavior are the α_2-noradrenergic subtype (13). The radioligand binding to this receptor in the PVN is dramatically affected by food deprivation, refeeding and circulating glucose (7, 21–23), which also affect the release of endogenous NE in the PVN (19, 44, 52, 53). The role of the α_1-receptor subtype in feeding has received little attention. While little change in this receptor has been detected in response to food deprivation or refeeding (21), a recent pharmacological study indicates that injection of an α_1-receptor agonist into the PVN actually causes a suppression of food intake (55).

The purpose of this study was to examine, using radioligand binding techniques, both the α_2- and the α_1-noradrenergic receptors in discrete hypothalamic nuclei, and determine whether their ability to bind to hypothalamic receptors is altered in obese Zucker rats. These animals were examined under ad lib feeding conditions, as well as after a period of food deprivation. The results of this experiment, described in preliminary form (17), reveal disturbances in both the α_2- and α_1-receptors, specifically in the PVN, of the obese rats (fa/fa) compared to the lean rats

(FA/−). They also demonstrate differential responsiveness of these receptors in the obese animals to the effects of food deprivation.

METHOD

Animals

Female lean (FA/−) and genetically obese Zucker rats (fa/fa) were used in this experiment. The animals were bred in a colony maintained at the Northeastern Ohio Universities College of Medicine, and were descendants of rats originally purchased from the Harriet G. Bird Memorial Labs, Stow, MA. The median age of these rats at the time of sacrifice was 14 months. All subjects were maintained on Purina rat chow and water ad lib. The rats were individually housed and kept on a 12:12 h light:dark cycle, with lights on at 0600 h. The animals were separated into 4 groups, 2 groups of lean rats and 2 groups of obese rats, with 8 animals per group.

Procedures

A group of lean and a group of obese rats were maintained ad lib on food and water until 48-h prior to sacrifice, when each group of rats was divided into ad lib and 48-h food-deprived subgroups. Water was continuously available to all animals. Rats were sacrificed between 0900–1100 h.

Tissue Preparations

All of the rats were sacrificed by decapitation, and their brains were rapidly removed and frozen on dry ice. Serial brain sections of 300 μm were cut in a cryostat, and 7 hypothalamic areas were microdissected, namely, the PVN, ventromedial hypothalamus (VMH), dorsomedial nucleus (DMN), medial preoptic nucleus (POM), perifornical lateral hypothalamus (PFH), supraoptic nucleus (SON), and arcuate nucleus-median eminence (ARC-ME).

Radioligand Binding Procedures

α_1- and α_2-Noradrenergic receptor binding assays were performed on the 7 hypothalamic sites. The α_1-receptors were examined through the specific binding of the α_1-noradrenergic receptor antagonist, [^{3}H]prazosin (18.8 Ci/mmole, New England Nuclear). For the α_2-receptors, the α_2-noradrenergic receptor agonist, [^{3}H]p-aminoclonidine ([^{3}H]PAC; 40–42.2 Ci/mmole, New England Nuclear), was used. The receptor binding methods for [^{3}H]prazosin and [^{3}H]PAC were, respectively, those of Greengrass and Brenner (14) and Rouot and Snyder (47), with some modification for micropunched tissue (21,35).

Tissue samples were homogenized in 0.05 M Tris-HCl buffer (pH 7.7), which for the [^{3}H]PAC binding assay also contained 10 mM $MgCl_2$. The homogenate was preincubated for 20 min at room temperature (25°C) and then incubated with either [^{3}H]PAC or [^{3}H]prazosin for 30 min at 25°C, in the presence or absence of phentolamine (50 μM, Regitine, CIBA). The homogenate was then placed in an ice bath to terminate the binding process. The samples were subsequently filtered and washed three times with ice cold Tris-HCl buffer (pH 7.7) and then counted for radioactivity in a scintillation counter. Specific binding was defined as the difference in radioactivity measured with and without phentolamine. Protein content of the homogenate was determined, in 50 μl aliquots, by the method of Bradford (4). The results were expressed as the quantity of ligand ([^{3}H]prazosin or [^{3}H]PAC) specifically bound in fmoles/mg protein.

Previous studies have provided evidence that [^{3}H]PAC, at a concentration of 2 nM, binds to the high affinity form of the α_2-receptor site (21). Recent investigations indicate that [^{3}H]PAC may also bind to certain nonadrenergic binding sites, namely, imidazoline-preferring receptors in the bovine brain (12). The possibility that [^{3}H]PAC in the present studies is binding primarily to α_2-noradrenergic, rather than to imidazoline-preferring receptor sites in the hypothalamus is supported by the evidence that: a) imidazoline-preferring receptors exist in certain extrahypothalamic regions but not in the hypothalamus of the rat brain (25); and b) the binding of the radioligand [^{3}H]idazoxan, which has affinity for both α_2- and imidazoline-preferring receptors (29), is completely displaced by norepinephrine in hypothalamic nuclei, and is altered in relation to the circadian cycle and nutritional state in a similar fashion to [^{3}H]PAC (21, 24, 27). While this assay procedure, therefore, very likely reflects binding to α_2-noradrenergic receptors, it does not distinguish between the pre- and postsynaptic receptor sites.

The specific [^{3}H]PAC binding (fmoles/mg protein) to α_2-receptors and [^{3}H]prazosin (fmoles/mg protein) to α_1-receptors in discrete hypothalamic areas were statistically analyzed using analysis of variance and post hoc comparisons (Duncan's New Multiple Range test) or Student's *t*-tests for direct comparisons between individual scores.

RESULTS

Figure 1 presents the results obtained with [^{3}H]PAC binding to the α_2-noradrenergic receptors in the hypothalamic regions of lean and obese rats under freely feeding conditions. These results revealed a difference in α_2-receptor binding in only one the 7 areas examined in these two genetic strains. This was the PVN, where 76% greater binding of [^{3}H]PAC to α_2-receptors of the obese rats compared to the lean rats ($p<0.05$) was detected. No significant differences in [^{3}H]PAC binding, between the lean and obese rats, were detected in any other hypothalamic site examined. A similar result was obtained with analysis of specific [^{3}H]prazosin binding to hypothalamic α_1-receptors of lean and obese Zucker rats under ad lib feeding conditions. As illustrated in Fig. 2, the PVN was distinguished, once again, as showing greater α_1-receptor binding (+89%; $p<0.05$) in the obese relative to the lean rats. No other hypothalamic nuclei exhibited a difference between these genetic strains.

In addition to these differences in baseline levels of α-noradrenergic receptor binding, the lean and obese rats exhibited differences in their responsiveness to 48 h food deprivation. With respect to specific [^{3}H]PAC binding to α_2-receptors, the lean rats (Fig. 3, top panel) exhibited little change after deprivation; only in the PVN was a small (−44%; $p<0.10$) decline in α_2-receptor binding detected. This is in contrast to the obese rats (Fig. 3, bottom panel), which demonstrated a significant decline in the α_2-receptor binding specifically in the PVN (−71%; $p<0.01$) as well as in two basal hypothalamic areas, namely, the SON (−58%; $p<0.01$) and ARC-ME (−66%; $p<0.01$). The remaining hypothalamic areas of the lean and obese rats failed to show any significant alterations in α_2-receptor binding after 48 h food deprivation.

As shown in Fig. 4, the α_1-receptor binding was less responsive than the α_2-receptor binding to the effects of food deprivation. In the lean rats, no differences between the satiated and deprived conditions were seen. Only in the obese rats was food deprivation associated with a significant decline in α_1-receptor binding; this occurred in only one area, namely, the PVN (−65%; $p<0.05$).

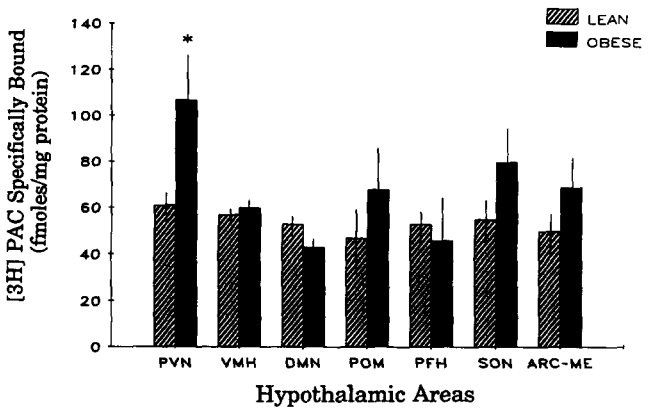

FIG. 1. [^{3}H]P-Aminoclonidine ([^{3}H]PAC) binding (fmoles/mg protein) to α_2-noradrenergic receptors in 7 discrete hypothalamic areas of lean (hatched bar) and genetically obese (solid bar) Zucker rats. A direct statistical comparison between the two groups revealed significantly higher [^{3}H]PAC binding only in the PVN of obese rats compared to their lean littermates (*$p<0.05$). Abbreviations: PVN, paraventricular nucleus; VMH, ventromedial hypothalamus; DMN, dorsomedial nucleus; POM, medial preoptic area; PFH, perifornical lateral hypothalamus; SON, supraoptic nucleus; ARC-ME, arcuate nucleus and median eminence.

DISCUSSION

α_2-Receptor Binding in Freely Feeding Lean and Obese Zucker Rats

In this study, elevated levels of α_2-receptor binding, specifically in the PVN, were detected in the genetically obese Zucker rats compared to the lean rats. A similar result has been obtained in Sprague-Dawley rats that became hyperphagic and obese on a high fat diet, as compared to rats that exhibited normal food intake and body weight gain on this diet (15). Greater binding to α_2-receptor in the PVN has also been seen in hyperphagic rats permitted to select from pure macronutrient diets (39). Moreover, an increase in hypothalamic α_2-receptor binding has been described in a different report in obese rats on a high-energy diet (37), although here the effect was seen not only in PVN, but also in other medial hypothalamic areas, including the VMN, DMN, and ARC, but not in the lateral hypothalamus.

This evidence is consistent with pharmacological results relating PVN α_2-receptors to eating behavior and energy expenditure (31). Both NE and the α_2-receptor agonist, clonidine, stimulate food intake in satiated rats, through their action on postsynaptic α_2-receptors located in the PVN (13, 30, 31). This stimulatory effect of clonidine is found to be significantly stronger in obese Zucker rats than in the lean rats (26), which may reflect the present biochemical finding that Zucker obese rats have greater α_2-receptor binding in the PVN. Since injection of NE into this nucleus also decreases energy expenditure (50), the reduced energy expenditure characteristic of the obese rat (5, 6, 40) may reflect the greater number of PVN α_2-receptor binding in conjunction with altered levels of PVN NE in female and male obese rats (8, 9, 38).

α_1-Receptor Binding in Freely Feeding Lean and Obese Zucker Rats

The increased α_1-receptor binding also detected in the PVN of obese Zucker rats agrees with the change seen in Sprague-Dawley rats made hyperphagic and obese on a high fat diet (15) and with the greater number of hypothalamic α_1-receptor binding detected in obese (ob/ob) mice compared to their lean littermates (45). This result, however, was not detected in another study in which the rats were made obese on a high sucrose/high fat diet; in these subjects, PVN α_1-receptor binding remained unaltered while VMH α_1-receptor binding was reduced (56). The significance of the changes observed in this receptor subtype need to be further examined in light of recent pharmacological

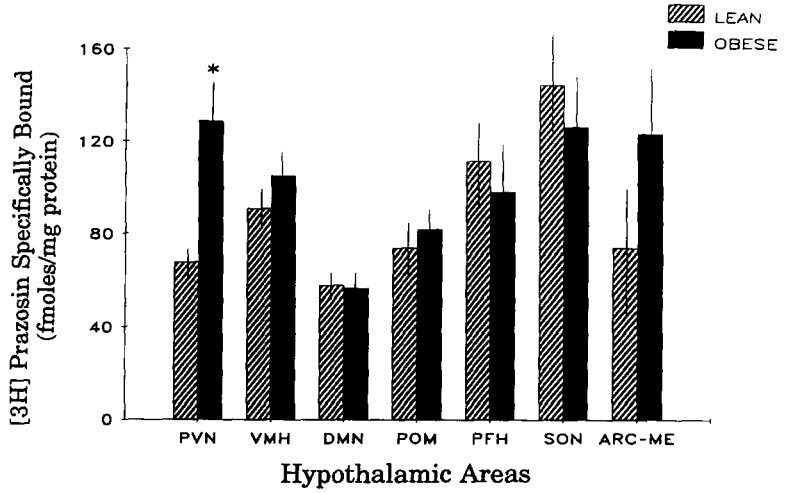

FIG. 2. [^{3}H]Prazosin (fmoles/mg protein) binding to α_1-noradrenergic receptors in 7 discrete hypothalamic areas of lean (hatched bar) and genetically obese (solid bar) Zucker rat. A direct statistical comparison between the two groups revealed significantly elevated levels of [^{3}H]prazosin binding exclusively in the PVN of obese rats as compared to their lean littermates (*$p<0.05$). (See legend to Fig. 1 for abbreviations.)

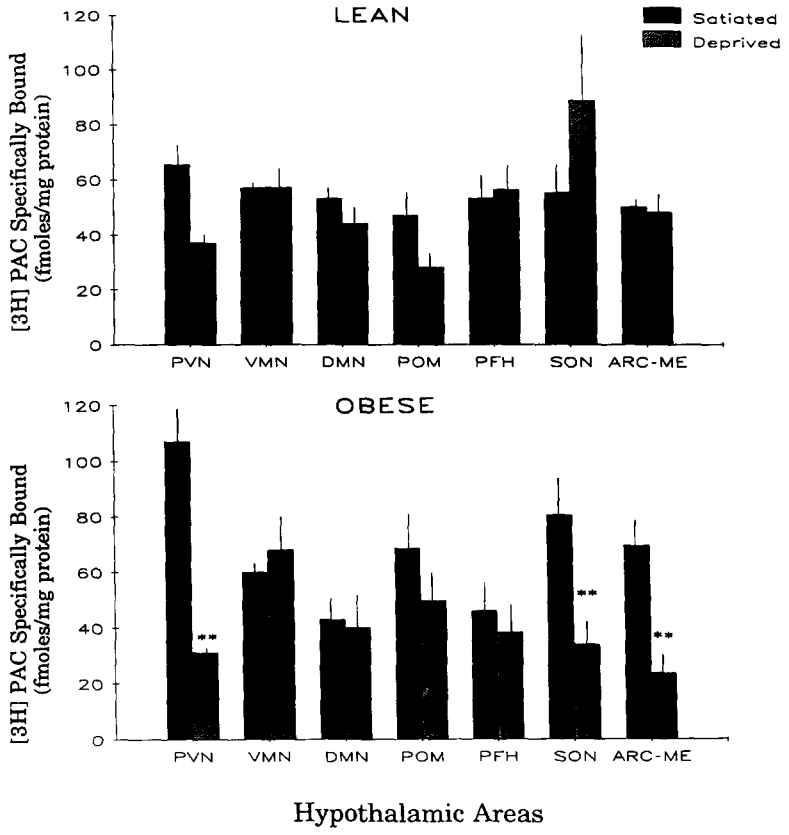

FIG. 3. Effect of food deprivation (48 h) on [^{3}H]p-aminoclonidine ([^{3}H]PAC) binding to α_2-noradrenergic receptors in 7 discrete hypothalamic sites of lean (top panel) and genetically obese (bottom panel) Zucker rats. Direct statistical comparisons between the satiated (solid bar) and food-deprived (hatched bar) rats revealed decline in α_2-noradrenergic receptors specifically in the PVN of obese (**$p<0.01$) rats. Also, a significant decline following food deprivation was seen in the SON (**$p<0.01$) and ARC-ME (**$p<0.01$) of the obese rats. (See legend to Fig. 1 for abbreviations.)

evidence demonstrating an inhibitory effect of an α_1-receptor agonist on food intake (55).

α-Receptor Binding in Food-Deprived Lean and Obese Zucker Rats

In addition to exhibiting higher baseline levels of α_2- and α_1-receptor binding in the PVN, the obese Zucker rats also showed greater changes in their α-receptors than the lean rats in response to food deprivation. In contrast to the lean subjects, which exhibited only a small decrease in PVN α_2-receptor binding after deprivation, the obese rats demonstrated a marked decline in [^{3}H]PAC binding in the PVN, as well as in the ARC-ME and SON. A decrease in α_2-receptor binding in the PVN is consistent with the results of two prior studies in Sprague-Dawley rats, which demonstrated a reduction in α_2-receptor binding in the medial hypothalamus (7), as well as selectively in the PVN (21,23), after 6 h and 48 h deprivation. These studies, consistent with the present results, demonstrated no change in α_2-receptor binding in the lateral hypothalamus or in the perifornical region of this structure, confirming the importance of the medial hypothalamus in this phenomenon. The decline in α_2-receptor binding seen in the basal hypothalamic nuclei, ARC-ME and SON, of the obese rats was not detected in either the lean rats of this study or in normal weight Sprague-Dawley rats (21).

The failure to observe any change in α_1-receptor binding after deprivation in lean rats agrees with previous studies showing no change in α_1-receptor binding following 48 h food deprivation, in either medial or lateral hypothalamic tissue of Sprague-Dawley rats (21). Also, no change in α_1-receptors in the basal hypothalamus following long-term food deprivation was seen (51). However, the obese rats of this study were unique in exhibiting a reliable decline in PVN α_1-receptors after deprivation. The relationship between this finding and the evidence suggesting that PVN α_1-receptors inhibit feeding behavior (55) remains to be determined.

Interaction Between Neuroendocrine Parameters and α_2-Receptors

A relationship between circulating levels of the glucocorticoid hormone, CORT, and the α_2-noradrenergic receptors in the PVN controlling food intake has been established biochemically as well as pharmacologically. In the Sprague-Dawley rat, adrenalectomy has been shown to reduce PVN α_2-receptor density while abolishing PVN NE-induced feeding, and CORT replacement reverses these effects (10, 20, 46). This relationship may the obese rat, which may be a consequence of the higher circu-

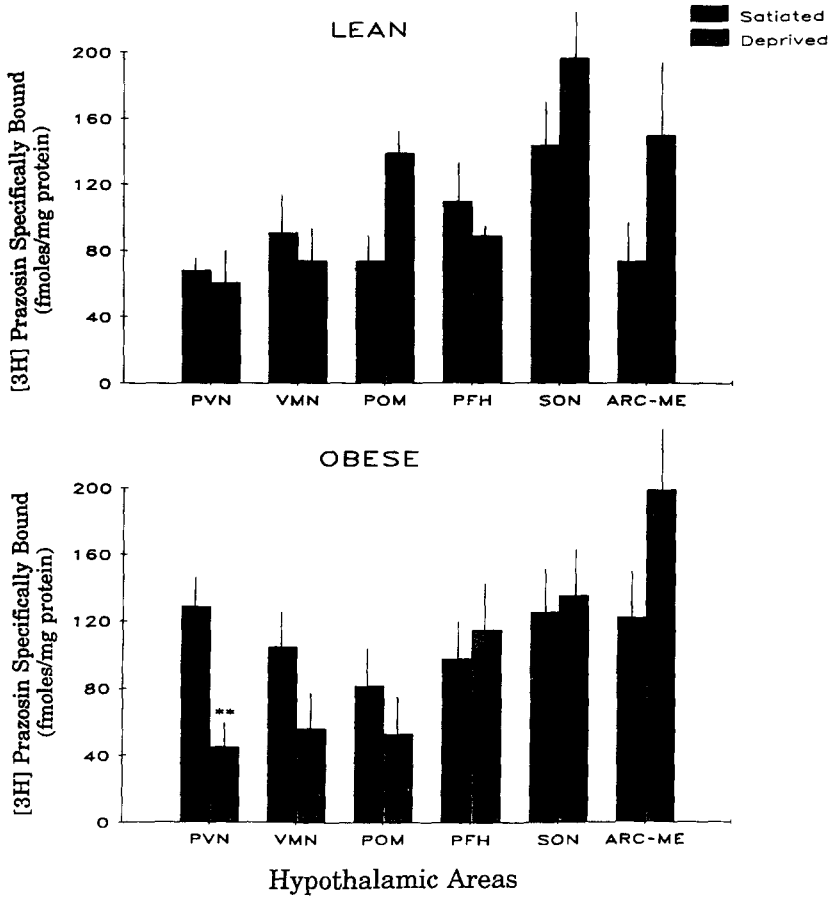

FIG. 4. Effect of food deprivation (48 h) on [^{3}H]prazosin binding to α_1-noradrenergic receptors in 7 discrete hypothalamic sites of lean (top panel) and genetically obese (bottom panel) Zucker rats. Direct statistical comparisons between the satiated (solid bar) and food-deprived (hatched bar) rats revealed a significant decline (**$p<0.01$) in α_1-noradrenergic receptors specifically in the PVN of the obese rats, with no such change in lean rats. (See legend to Fig. 1 for abbreviations.)

lating levels of CORT observed in these animals (16,41). The hyperphagia and obesity observed in animals has been linked to the adrenal steroids (5, 6, 40), and the reversal of the obesity syndrome after removal of the adrenal glands may, in part, reflect the downregulation of the PVN α_2-receptors (20).

The α_2-receptors also appear to be related to glucoregulatory processes. A positive correlation between circulating glucose levels and [^{3}H]PAC binding has been detected in the medial hypothalamus, in particular the PVN, in animals injected with tolbutamide (7,22) or after food deprivation (23). Moreover, administration of NE to the PVN stimulates the release of glucose (7) and inhibits the firing of hypothalamic glucose-sensitive neurons (28). Thus it is possible that the differences seen between the obese and lean Zucker rats, in terms of their PVN α_2-receptor binding under satiated and deprived conditions, may reflect the differences between these genetic strains in their sensitivity to insulin or in their glucose tolerance.

Physiological Significance of Changes in α-Noradrenergic Receptors

Similar to the present report, other investigations in obese Zucker rats have detected disturbances in the activity of various neurochemical systems that have been associated with a potentiation of food intake, in particular, of energy-rich diets (31,32). In the obese animals, studies have identified higher PVN levels of the peptide neuropeptide Y (1), increased gene expression for neuropeptide Y in the hypothalamus (34) or arcuate nucleus (48), and an increase in hypothalamic mRNA for the peptide galanin (18).

An important question to be addressed in these studies is whether these neurochemical disturbances in the genetically obese rat are a cause, a promotor, or a consequence of the hyperphagia and obesity. It is now clear that genetically obese rats display phenotypic and metabolic variations very early in life, between 2 days and 3 weeks of age, with respect to their blunted thermogenesis, larger white adipocytes, hyperinsulinemia, hyperphagia, and increased body weight (2, 3, 5, 6, 40, 42, 43). In terms of the ratio of food intake/body weight, differences between the lean and obese rats can be seen shifting from a higher ratio in the obese at 3–10 weeks of age, to equal ratios at 13–18 weeks, and then to a below normal ratio in the obese after 19 weeks (11).

The present study, as well as those of others (1, 8, 9, 18, 34, 38), examined Zucker rats older than 2 months of age, at a time when most symptoms of the syndrome had been expressed.

Thus it is possible that the observed changes in the brain neurochemical systems are actually a consequence of the hyperphagia and/or obesity. To assess this, the neurochemical systems of these animals need to be examined at different stages of development. The importance of this is underscored by the study of Levin and Sullivan (38), which at different ages revealed changing NE levels in the PVN of the obese relative to the lean rats, and by the recent studies of Jhanwar-Uniyal et al. (18) and Leibowitz et al. (34), showing differences between the lean and obese rats, in gene expression for neuropeptide Y and galanin, that vary with age. Whereas higher levels of mRNA for neuropeptide Y and galanin were detected in the obese rats at 40 weeks of age, at 11 weeks this pattern was not detected, and, in fact, a lower level of galanin mRNA was observed in the obese Zucker rats.

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