Proceedings of the National Academy of Sciences
Vol. 68, No. 2, pp. 332–334, February 1971

Hypothalamic Alpha- and Beta-Adrenergic Systems Regulate Both Thirst and Hunger in the Rat

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Communicated by Neal E. Miller, November 30, 1970

ABSTRACT **Adrenergic and adrenolytic drugs were injected directly into the hypothalamus of the rat brain through permanently implanted cannulas and were found to have reliable effects on water consumption in water-satiated and water-deprived subjects. The beta-adrenergic agonist stimulated thirst, and the beta-adrenergic blocker suppressed thirst. Conversely, the alpha-adrenergic agonist suppressed thirst, and the alpha-adrenergic blocker enhanced thirst. These results demonstrate the existence of a hypothalamic beta-adrenergic "thirst" system which opposes a hypothalamic alpha-adrenergic "water-satiety" system. In view of our earlier results demonstrating the existence in the hypothalamus of an alpha-adrenergic "hunger" system which opposes a beta-adrenergic "food-satiety" system, we suggest that a reciprocal inhibitory relationship between these adrenergic hunger- and thirst-regulating systems provides a neurochemical explanation for the ability of organisms to maintain food and water consumption at a constant ratio. In the regulation of both hunger and thirst, the central cholinergic system mimics the hypothalamic beta-adrenergic system and opposes the hypothalamic alpha-adrenergic system.**

Earlier investigations of how adrenergic drugs affect food intake when injected peripherally (1) and when injected hypothalamically (2–4) have shown that hunger in the rat is regulated by two hypothalamic antagonistic systems, an alpha-adrenergic "hunger" system, which elicits eating behavior, and a beta-adrenergic "food-satiety" system, which suppresses eating behavior. Because of the close relationship that is known to exist between hunger- and thirst-control, these studies with adrenergic agents were extended in order to investigate the central neurochemical regulation of thirst, as well as the central neurochemical basis for the interaction between hunger and thirst.

Grossman (2) found that hypothalamic injections of norepinephrine, an alpha-adrenergic stimulant, suppressed water consumption in water-deprived rats. Lehr and his colleagues (5) showed that peripheral injections of isoproterenol, a beta-adrenergic stimulant, enhanced water consumption and that this effect was blocked by peripheral injection of a beta-adrenergic blocker. These authors considered their results "to be consistent with the concept of direct or reflex activation of central mechanisms of body water regulation." In an attempt to provide central evidence for this suggestion, they applied isoproterenol crystals to selected brain sites through chronically implanted cannulas but were unsuccessful in obtaining a reliable drinking response. Subsequently, other investigators suggested that this drinking effect induced by systemic isoproterenol was actually mediated by peripheral mechanisms (6).

In order to obtain direct evidence for a central adrenergic thirst-regulating mechanism, suggested by Lehr (5) on the basis of indirect evidence, we injected solutions of alpha- and beta-adrenergic agonists and blockers into the lateral hypothalamus and tested their effects on water consumption. The lateral hypothalamus was chosen as our first site for investigation because of the role it is known to play in the regulation of both thirst and hunger. Small lesions in this hypothalamic area have been shown to produce adipsia, whereas electrical stimulation of the same region has been shown to elicit water intake (7, 8). As a result of our central pharmacological investigations, we found that lateral hypothalamic injections of both alpha- and beta-adrenergic and adrenolytic drugs do indeed reliably influence the intake of water. Our findings showed that in the regulation of thirst, as in the regulation of hunger (3), hypothalamic alpha- and beta-adrenergic receptors function antagonistically, and, on the basis of these results, we suggest that hypothalamic alpha-beta antagonism explains neurochemically how hunger and thirst, as regulated by the brain, may interact so that food and water consumption are kept in constant balance.

MATERIALS AND METHODS

Placement of cannulas

42 male albino Sprague-Dawley rats (weight approximately 320 g) were used in these experiments. They were all stereotaxically implanted with unilateral chronic cannulas under Nembutal anesthesia, according to the procedure described by Slangen and Miller (9). All placements were aimed at the lateral hypothalamus, which, with skull flat, had coordinates of 2.8 mm behind bregma, 1.5 mm lateral, and 8.5 mm vertical.

General procedure

All rats were maintained and tested on Purina lab chow and water. 21 rats were tested on all drugs while water- and food-satiated, and 21 others were tested on all drugs when they had been deprived of water (though not of Purina chow) for 18 hr. The deprivation period extended from 4:00 p.m. on the day before the test day until 10:00 a.m. the next morning. Upon completion of each test, these rats received water and food *ad lib.* until their next period of deprivation. All tests were made in the morning, every 2–4 days, and consisted of measuring the amount (in milliliters) of water consumed by the rats from a calibrated water tube during the first 90 min after drug injection. Food was not available during the test period.

Control tests, in which the rats were injected with only the control medium (saline), were interspersed between the drug tests according to a Latin-square sequence. All the rats were

carried through the entire series of drug injections, in which the following drugs were used: (*1*) *l*-Norepinephrine bitartrate (20 μg). In the peripheral nervous system, this drug is known to have primarily alpha-adrenergic activity, except with respect to the heart, where it acts as a beta-adrenergic agonist (10). In the central nervous system, norepinephrine also appears to be primarily alpha-adrenergic, although under special circumstances, such as in the presence of an alpha blocker and at higher doses, we have found that norepinephrine has some beta-adrenergic activity in the hunger-regulating system. Because of the relatively low dose used here, the present study is concerned only with norepinephrine's alpha-adrenergic action. (*2*) *l*-Isoproterenol bitartrate (40 μg). In the periphery, as well as the brain, isoproterenol appears to have only beta-adrenergic activity (3, 4, 10). (*3*) Phentolamine hydrochloride (102 μg), an alpha-adrenergic blocker. (*4*) Propranolol hydrochloride (84 μg), a beta-adrenergic blocker. (*5*) Carbamylcholine chloride (carbachol; 0.5 μg), a potent cholinergic stimulant.

All drugs, except phentolamine, were dissolved in normal saline and injected directly into the lateral hypothalamus via the same cannula in a volume of 0.4 μl. Phentolamine hydrochloride was dissolved in distilled water and, because of its lower solubility, had to be injected in a volume of 4 μl.

RESULTS

In general, our results showing the effects of alpha- and beta-adrenergic, as well as cholinergic, drugs on water intake demonstrate that: (*1*) The hypothalamus contains a beta-adrenergic "thirst" system, which when stimulated elicits drinking behavior, and an alpha-adrenergic "water-satiety" system, which when stimulated suppresses drinking behavior; and (*2*) The central cholinergic system functions in opposition to the alpha-adrenergic system of the hypothalamus and therefore mimics the effects of the hypothalamic beta-adrenergic system.

In detail the results are as follows: (*1*) Water intake of the satiated and the water-deprived rats was in all cases similarly affected by a given drug. (*2*) Norepinephrine, the alpha-adrenergic agonist, suppressed water intake by 5.0 ml (32%) in water-deprived rats ($P < 0.01$). In satiated rats, the reduction in water intake induced by norepinephrine was not statistically significant because of the already very low water intake (0.7 ml) by satiated, saline-injected rats. (*3*) Isoproterenol, the beta-adrenergic agonist, enhanced water intake by 6.3 ml in satiated rats ($P < 0.01$) and by 2.4 ml in water-deprived rats ($P < 0.05$). (*4*) Similarly, carbachol, the cholinergic stimulant, increased water intake by 4.4 ml in satiated rats ($P < 0.01$) and by 4.7 ml in water-deprived rats ($P < 0.01$). (*5*) Phentolamine, the alpha-adrenergic blocker, enhanced water intake in satiated rats by 3.4 ml ($P < 0.01$) and by 3.6 ml in water-deprived rats ($P < 0.01$). (*6*) Propranolol, the beta-adrenergic blocker, suppressed water consumption by 2.0 ml (15%) in water-deprived rats ($P < 0.05$). In satiated rats, the reduction in water intake was not statistically significant, because of the already very low intake by controls (0.6 ml).

DISCUSSION

Our findings provide strong evidence for the existence in the hypothalamus of antagonistic adrenergic thirst-regulating receptors. The beta receptors are part of a system that enhances water consumption, and when this beta "thirst" system is blocked by a beta blocker, water consumption is suppressed. In contrast, the alpha receptors are part of a system that suppresses water consumption; when this alpha "water-satiety" system is blocked by an alpha blocker, water consumption is enhanced. The fact that in both systems the adrenergic blocker produces effects opposite to those produced by its corresponding agonist supports the hypothesis that antagonistic beta and alpha mediation is a normal physiological property of the hypothalamic thirst-regulating mechanism.

These results suggest that the drinking response induced by peripherally-injected isoproterenol (5) may be at least partially mediated by central mechanisms, as suggested by Lehr. Our results further indicate that these central mechanisms might be located in the lateral hypothalamus. Finally, our recent findings (to be published), showing that the thirst-stimulating effect of central isoproterenol is prevented by a centrally-injected beta blocker and the thirst-suppressing effect of central norepinephrine is prevented by a centrally-injected alpha blocker, provide confirmatory evidence that the "thirst" system is indeed beta-adrenergic and the "water-satiety" system is indeed alpha-adrenergic.

Now that a neurochemical basis for hypothalamic regulation of thirst is identified, it becomes apparent how this system and the hypothalamic hunger system, consisting of neurons with alpha "hunger" and beta "food-satiety" receptors (3), interact antagonistically so that food and water consumption are maintained at a constant ratio. A reciprocal inhibitory relationship exists between the adrenergic hunger- and thirst-regulating systems; the inhibitory interaction, in which the alpha transmitter functions simultaneously as a hunger stimulator and a thirst suppressor, keeps feeding behavior active while drinking behavior is inhibited, and the converse interaction, in which the beta transmitter functions simultaneously as a thirst stimulator and a hunger suppresser, keeps drinking behavior active while feeding behavior is inhibited.

Our results showing that lateral hypothalamic injections of the cholinergic agent, carbachol, enhance water consumption in satiated and water-deprived rats confirm earlier findings of Grossman (2). We replicated another experiment carried out earlier by Grossman (2), in which food-deprived rats were injected with carbachol. We found, as did Grossman, that food intake was significantly reduced ($P < 0.01$). Grossman suggested (11), on the basis of these and his results on the hunger-stimulating and thirst-suppressing effects of norepinephrine, that a central cholinergic drinking mechanism and a central adrenergic feeding mechanism interacted in an inhibitory fashion; when one mechanism became active, it inhibited the other. He suggested that this reciprocal inhibition between cholinergic and adrenergic systems accounted for the constancy of the animal's food/water ratio.

On the basis of our recent evidence for central alpha- and beta-adrenergic systems, Grossman's hypothesis concerning the interaction between cholinergic and adrenergic control of ingestive behavior can now be modified. In the regulation of both hunger and thirst, we have found that the central cholinergic system opposes only the central alpha-adrenergic system. It does not oppose the central beta-adrenergic system but instead produces effects similar to those produced by the beta-adrenergic system. In the peripheral nervous system, adrenergic–cholinergic antagonism is well established. There appear to be, however, a few cases, such as in the regulation of blood vessel constriction in skeletal muscle, where the cholinergic

system mimics the beta-adrenergic system and opposes the alpha-adrenergic system (10). The adrenergic–cholinergic antagonism we have found in the hypothalamus appears to be of this nature.

Essentially, there appears to exist in the brain a dual-control neurochemical mechanism for thirst-stimulation plus hunger-suppression which consists of beta-adrenergic and cholinergic receptor systems. We have recently investigated whether these two neurochemical systems operate in an independent parallel fashion, or whether one system mediates the actions of the other, and our preliminary evidence, which shows that both beta-adrenergic thirst and carbachol thirst are blocked by a beta-adrenergic blocker but that *only* carbachol thirst is blocked by a cholinergic blocker, suggests that the hypothalamic beta-adrenergic "thirst" system mediates the drinking response induced by carbachol. Whether or not a similar dual-control mechanism exists for hunger stimulation plus thirst suppression, consisting of an alpha-adrenergic system and either a different type of cholinergic action or an entirely different transmitter system, has yet to be determined.

It is interesting to note the experiments of Margules (12), in which he tested the effects of hypothalamically-injected adrenergic drugs on milk intake in rats. He found that norepinephrine suppressed milk intake in satiated rats and that phentolamine, the alpha blocker, enhanced milk intake in deprived rats. Margules interpreted these results as demonstrating an adrenergic food-satiety system. Since we have found that *water* intake is suppressed by norepinephrine and enhanced by phentolamine, in contrast to the intake of food pellets, which is enhanced by norepinephrine and suppressed by phentolamine, we suggest that Margules' studies measuring the intake of milk are actually measuring thirst as opposed to hunger.

Earlier experiments designed to localize within specific areas of the hypothalamus the alpha- and beta-adrenergic hunger-regulating systems have shown that the alpha "hunger" receptors are predominantly located in, and act to inhibit, the ventromedial "satiety" area, and the beta "food-satiety" receptors are predominantly located in, and act to inhibit, the lateral "feeding" area (4). Our preliminary results from similar studies on water consumption suggest that the thirst-regulating neurons with alpha-adrenergic, beta-adrenergic, and cholinergic receptors are differentially concentrated in different parts of the hypothalamus.

I am grateful to Miss Elizabeth Sherwood for her excellent technical assistance and to Dr. N. E. Miller for his helpful criticisms of the manuscript. I also thank Ayerst Laboratories, Sterling-Winthrop Research Institute, and Ciba Pharmaceuticals for their generous supply of drugs. This work was supported by USPHS grant MH 13189 and by a grant from Hoffmann-La Roche.

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