Noradrenaline-induced feeding responses in the rat do not depend on food characteristics

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The noradrenergic system of the hypothalamic paraventricular nuclei (PVN) has been associated with feeding, but whether it controls feeding in a way that is relevant to energy balance is still unclear. Rats were maintained on a high energy, carbohydrate-rich diet (HC), or a low energy, carbohydrate-free, protein-rich diet (LP), until their daily energy intakes equalized. When injected with noradrenaline (NA) into the PVN, they ingested the same amounts of both diets so that the animals on the LP diet consumed only half the total energy of those on the HC diet. Continuous delivery of NA into the PVN *via* a microdialysis probe induced chewing on non-nutritive pieces of corks. The same chewing pattern could again be elicited by the subsequent NA deliveries. It is concluded that the nutritional value of a diet is irrelevant to the NA feeding response. The failure of NA administration to increase rat feeding in terms of energy intake, combined with its ability to stimulate chewing, suggests that the primary role of the NA system of the PVN may not be controlling the carbohydrate and energy intake, but rather gating behavioral responses that under appropriate circumstances may lead to ingestion.

Key words: feeding behavior, gnawing, chewing, energy balance, mastication, gating, norepinephrine

INTRODUCTION

The noradrenergic system of the hypothalamic paraventricular nuclei (PVN) has long been implicated in mediating feeding behavior (Grossman 1962, Booth 1967, Aravich et al. 1982, Fukushima et al. 1987, Peinado and Myers 1987). The acute administration of noradrenaline (NA) into the PVN reliably evokes feeding in satiated rats (Leibowitz 1975, Matthews et al. 1986), whereas chronic infusions of NA enhance both food intake (increase in the size and rate of meal ingestion), and body weight (Ritter and Epstein 1975, Leibowitz et al. 1984). These responses are mediated by α_2-noradrenergic agonists, and blocked by α_2-noradrenergic antagonists as well as by discrete lesions of the PVN (Goldman et al. 1985, Shor-Posner et al. 1985). The PVN noradrenergic system also interacts with other cerebral neural circuits and the endocrine system, that together are involved in the regulation of body energy stores (Smythe et al. 1984,

Peinado and Myers 1987, Rothwell 1990, Richard 1993, Cabanac and Richard 1995). Moreover, NA administration seems to augment, in a selective way, the intake of carbohydrates, or foods rich in carbohydrates, while also suppressing protein consumption (Leibowitz et al. 1985). These well documented findings suggest that the noradrenergic system of the paraventricular hypothalamus is involved in the control of the intake of specific dietary nutrients, especially carbohydrates (Yee et al. 1987), as well as in the control of total energy consumption (Yee et al. 1987). However, the involvement of this system in affecting feeding does not necessarily mean that NA in the PVN specifically controls food intake in a way that is relevant to the maintenance of energy balance. In fact, although it is relatively easy to affect the amount of food eaten, little is known about the mechanisms controlling energy intake. Some of the paradoxical findings are that NA injections into the PVN stimulate oral non-ingestive responses rather than feeding ingestive responses, or that during short-term feeding rats do not control energy intake (Matthews et al. 1986, Swiergiel and Peters 1987, Swiergiel and Cabanac 1989).

Therefore, it is possible that the stimulation of the PVN induces a state of general arousal, which can change animal motivation and lead to a wide-range of arousal-oriented behaviors (Valenstein et al. 1970). These types of behaviors include emotional responses (Aston-Jones et al. 1999, Berridge and Waterhouse 2003), predatory attack (Bhatia et al. 1997), defensive responses (Barrett et al. 1987, 1990), male and female reproductive behavior (Caggiula et al. 1976, Nock and Feder 1979), and feeding and drinking responses (Valenstein et al. 1969). Furthermore, NA reaching the PVN can stimulate corticotropin-releasing factor (CRF) release and, through this mechanism, activate the hypothalamic-pituitary-adrenal axis (Koob 1999, Ziegler et al. 1999, Avraham et al. 2002) and stress-related behavioral responses (Swiergiel et al. 1996, Dunn and Swiergiel 2008, Swiergiel et al. 2008).

In the present study, an attempt was made to dissociate the intake of food mass from the intake of metabolizable energy during a single, short-term meal triggered by the administration of NA into the PVN. Furthermore, ingestive responses were compared with oral, non-ingestive responses. To this aim, the effects of NA administration into the PVN on the intake (mass and metabolizable energy) of diets with different nutritional composition and caloric density, and on the occurrence of behavioral patterns, in particular signs of general arousal and chewing of non-nutritive items were recorded.

METHODS

Animals

Outbred Wistar-Swiss male rats from the in-house animal breeding facility were maintained on a freely available rat diet (UAR/A04, France, chow pellets, energy content: 12.2 kJ/g) and on tap water for several weeks prior to experimentation. The rats were housed singly in an environmentally controlled room under a 08:00 AM–06:00 PM light/dark cycle. By the time of surgery the rats were 3 month old and weighed between 350–400 g. All experiments were carried out during the light period, between 11:00 AM and 01:00 PM, and in the animals' home cages. The experiments were carried out in accordance with the European Communities Council Directive (86/609/EEC) and protocols were approved by Animal Research Ethical Committee.

Diets

The experimental diets were hard, non-crumbling pellets for rats, custom-made by NAFAG, Switzerland. The high energy density diet (HC) was a modified NAFAG No. 900, composed of purified ingredients: 26% protein (casein calcium-vitamin free), 44.7% carbohydrate (corn and wheat starch, sucrose), 5.2% fat (soy oil), 9.3% crude fiber (mainly cellulose), 4.8% minerals and vitamins, 10% water, and provided 14.5 kJ/g of metabolizable energy. The low energy diet (LP) was a modified NAFAG No. 909 and its caloric content, in comparison with the high energy diet, was reduced by 50%. This "diluted" diet provided 7.3 kJ/g of ME (metabolizable energy) and was composed of the same components as the HC diet, but in the proportion of 29% protein, 5.5% fat, 47.3% fiber, 8.2% minerals, vitamins and bentonite, and 10% water. It was thus a protein- and fiber-rich, carbohydrate-free, diet (all carbohydrates removed and a considerable amount of nonnutritive fiber added). The specific gravity of the ground (or chewed by a rat) diets was 0.76 g/ml. Every day fresh pellets were placed in the hoppers. Spillage, if any, was accounted for when assessing food intake.

Surgery and histology

Under pentobarbital anesthesia (50 mg/kg), all rats were stereotaxically implanted with unilateral cannulae of 0.50 mm outer diameter to guide either an injector or a microdialysis probe. The tip of the cannula was aimed 1 mm above the dorsal aspect of the hypothalamic PVN. The following coordinates were used: 0.2 mm caudal to bregma, 0.4 mm lateral to midline, 6.2 mm below the skull surface, with the incisor bar raised 3.1 mm above the interaural line. The cannulae were fixed with stainless steel screws and dental cement to the skull. When not in use, the cannulae were occluded with stainless steel wire. After completion of the experiments, all rats received terminal pentobarbital anesthesia and were perfused with 10% formalin. Rat brains were sectioned coronally every 50 μm, stained with cresyl violet, and the placements of the cannulae tips were localized. Only data obtained from those animals whose infusion site clustered within the dorsal aspect of hypothalamic PVN are presented. Representative scheme of the microdialysis probes placement is presented in Fig. 1.
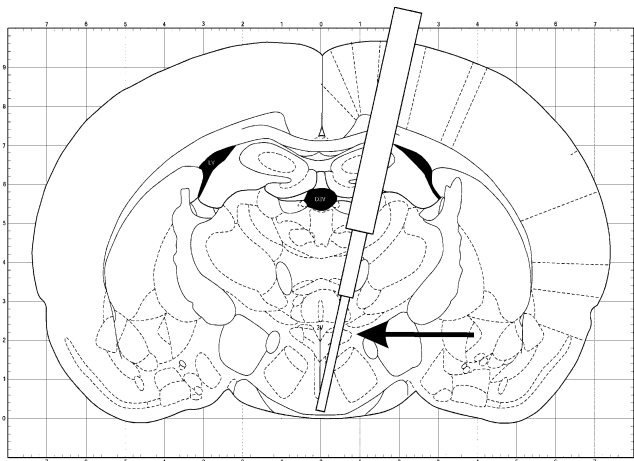
Fig. 1. Coronal section of the rat brain from the Paxinos and Watson atlas (bregma −1.80) indicating the approximate position of the microdialysis probes within hypothalamic PVN (black arrow) (according to Wieczorek and Dunn 2006, modified).
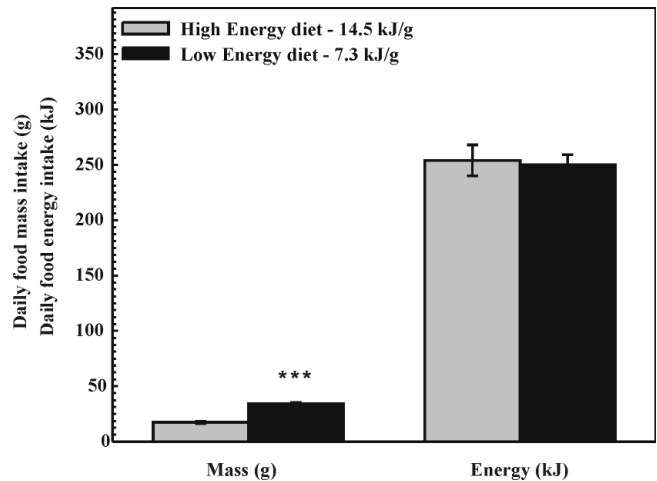

Fig. 2. Daily intake of food mass (g) and food energy (kJ) in rats maintained for 10 days on the low (LP) or high (HC) energy density diets. (***) Different from the HC diet group at $P<0.001$. Values are means ± SEM, $n=8$.

Experimental procedure

After a post-operative recovery period of ten days, all rats were screened for their feeding response to the PVN-NA injections. Intrahypothalamic injections of 0.4 µl of sterile vehicle (0.9% NaCl, 0.01% ascorbic acid; control) or NA solution (treatment) were given through the implanted cannula using an injector of 0.20 mm outer diameter and projecting 1.5 mm outside the cannula. The freshly prepared NA infusions contained 40 nmol of l-norepinephrine-d-bitartrate (Sigma) in 0.4 µl of vehicle, the same dose as in our previous experiments (Swiergiel and Peters 1987). These doses have been highly effective in stimulating food intake, are widely used, and produce robust responses (Goldman et al. 1985, Matthews et al. 1986, Swiergiel and Peters 1987).

One hour before the injections, each rat was weighed and handled. At the same time, overnight food leftovers were removed and the fresh food pellets given. This procedure ensured that the rats were satiated prior to infusions. At the end of the pre-infusion period the fresh food pellets were removed. The rat was then infused with either vehicle or NA, several pre-weighed, firm, and non-crumbling food pellets given, and food intake during the next 60 min recorded. All animals were tested for six consecutive days. On days 1, 3, and 5 vehicle was given, and on days 2, 4, and 6 NA was administered. Based on the results of the screening test, 16 rats with a consistent feeding response of 3.5 ±

0.5 g of food after NA, relative to 0.6 ± 0.3 g of UAR/ A04 chow after vehicle, were retained for further study. The pattern of drinking and feeding produced by NA injections closely resembled the feeding behavior described, in details, elsewhere (Leibowitz 1975, Swiergiel and Peters 1987). The rats were then randomly assigned to two groups and habituated to either HC diet or LP diet, until their daily energy intake equalized and became stable (Fig. 2). The effects of the NA or vehicle injections on a one-hour food mass and energy intake of either the concentrated or diluted diets were then recorded.

In a separate experiment, 6 naive rats were used to examine the effects of a slow (non-stressing) remote delivery of vehicle or NA into the PVN on behavior. First, six inedible pieces of cork were placed on the floor of a cage. Vehicle (artificial cerebrospinal fluid (aCSF) was prepared according to Sharp and coworkers (1989): 1.2 mM $CaCl_2$, 1.2 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, 3.4 mM KCl, 140 mM NaCl, pH 7.2) or NA (166 nmol/µl) were then continuously delivered into the PVN using a microdialysis probe equipped with 2 mm long working osmotic membrane (Cuprophane Pore Fiber, molecular weight cutoff 5 000–6 000 daltons). The probe was connected through a long (0.50 m) tubing to the swivel and then through another tubing (0.50 m long) to a syringe pump placed outside the cage. The flow of fluid through a probe was maintained at a rate of 2 µl/min. Approximately 40 nmol during the 2-min administration was deliv-
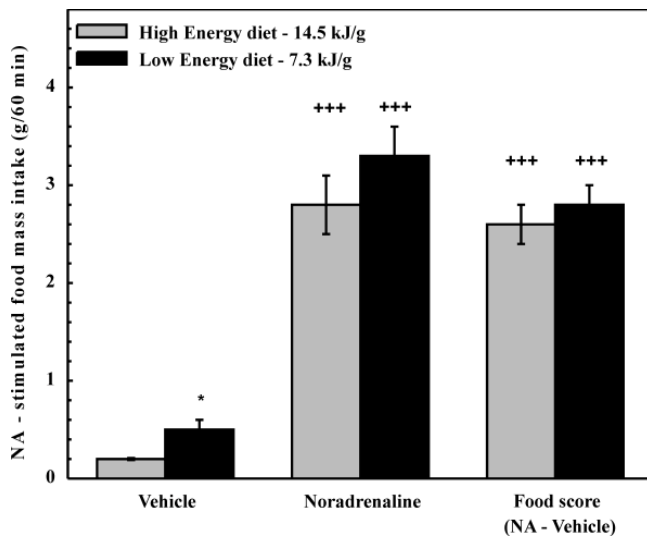
Fig. 3. Noradrenaline-stimulated (acute injections of NA into hypothalamic PVN) 1-hour food mass intake (g) of the low (LP) and high (HC) energy density diets. "Food score" is a difference between noradrenaline injection-induced feeding and vehicle injection-induced feeding. (*) Different from the HC diet group at $P<0.05$; (+++) Different from the "vehicle" values at $P<0.001$; $n=8$.
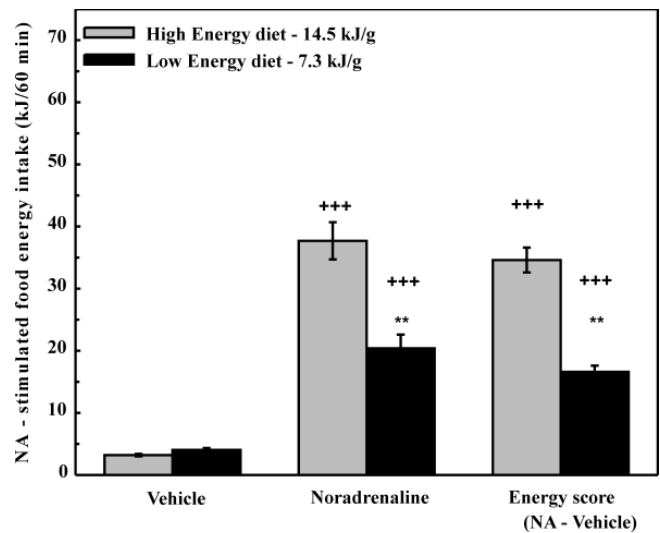

Fig. 4. Noradrenaline-stimulated (acute injections of NA into hypothalamic PVN) 1-hour food energy intake (kJ) of the low (LP) and high (HC) energy density diets. "Energy score" is a difference between noradrenaline injection induced feeding and vehicle injection-induced feeding. (**) Different from the HC diet group at $P<0.01$; (+++) Different from the "vehicle" values at $P<0.001$; $n=8$.

ered. (Assuming experimentally verified 12% recovery rate of NA *via* the probe, it means that only 12% of NA, dissolved in an artificial cerebro-spinal fluid crossed through a working, osmotic membrane of a microdialysate probe and then influenced surrounding tissue.) All experiments were videotaped and the number of cork chewing episodes, and the numbers of episodes of horizontal locomotor activity, rearing and wall climbing were scored during the 2-min infusion. Each rat in this experiment received a single infusion of either vehicle or NA in random order.

Statistics

Student *t*-test for independent variables was used to analyze food mass and energy intake in the first experiment, and for dependent variables to analyze rats' behavior in the second experiment.

RESULTS

After several days of diet habituation, the rats adjusted their 24-hour food intake to accommodate the differences in caloric content of the two diets (Fig. 2). On the 10th day of habituation, the animals on the LP

diet ate twice the amount of food eaten by the rats maintained on the HC diet (34.3 ± 1.2 vs. 17.5 ± 1.0 g; $t_{14}=9.45$, $P<0.001$), and as a result, the daily energy intake of the two groups of rats was almost identical (250 ± 9 vs. 254 ± 14 kJ).
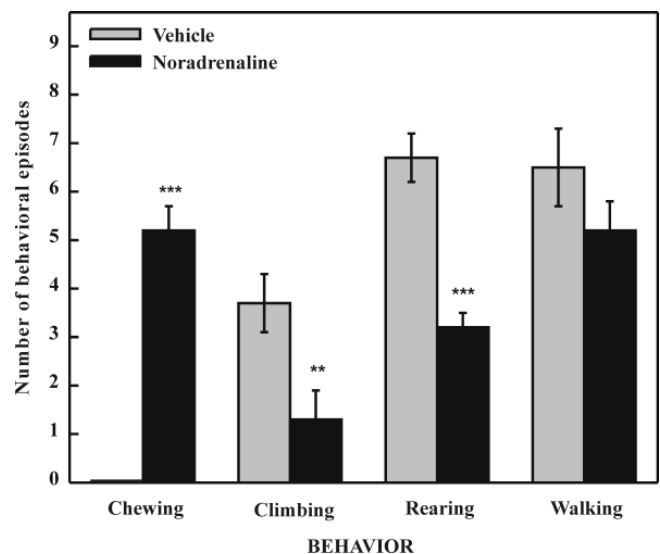

Fig. 5. Noradrenaline-stimulated (slow delivery of NA into hypothalamic PVN *via* a microdialysis probe) behavioral patterns (2-min score). (*); (***) Different from the vehicle group at $P<0.05$; $P<0.001$; $n=6$.

Short-term (1-hour) intake after the control vehicle injection was twice higher for rats fed the LP diet than that of rats fed the HC diet (0.5 ± 0.1 vs. 0.2 ± 0.1 g; t_{14}=2.41, P<0.05). After deducting this amount from the food intake recorded after the NA injections, it was found that NA evoked a similar (significant at t_{14}=5.78, P<0.001) net increase in 1-hour HC and LP food mass intake (2.8 ± 0.3 vs. 3.3 ± 0.3 g; Fig. 3).

Thus, the rats habituated and maintained on the high caloric diet consumed twice as much energy than those maintained on the low caloric diet (37.7 ± 3.0 vs. 20.4 ± 2.2 kJ; t_{14}=3.68, P<0.01; Fig. 4).

In the second experiment in which continuous NA was administered *via* a microdialysis probe, it was observed that approximately 10–15 s after the onset of NA delivery the rats would begin to chew the non-nutritive pieces of cork that were placed in their cages. Only NA delivery induced the cork-chewing episodes [0 ± 0 vs. 5.2 ± 0.5, Vehicle and NA, (t_{10}=10.826, P<0.001); Fig. 5]. NA did not affect the number of episodes of horizontal locomotor activity (6.5 ± 0.8 vs. 5.2 ± 0.6) but decreased vertical exploratory activity (number of episodes of wall climbing: 3.7 ± 0.6 vs. 1.3 ± 0.6; t_{10}=2.811, P<0.02, and free-standing rearing: 6.7 ± 0.5 vs. 3.2 ± 0.3; t_{10}=6.012, P<0.001). Approximately 2 min after the onset of NA administration, the rats would fall asleep. After a 5-min break in NA delivery, the same pattern of behavior could be induced with the next NA delivery but not with vehicle administration.

DISCUSSION

The results clearly demonstrate that noradrenaline (NA) injected into the hypothalamic paraventricular nucleus (PVN) induces a vigorous feeding response regardless of nutritional composition or caloric content of the diet. That is, NA injections evoked a similar increase in 1-hour food mass (or volume) intake of carbohydrate- and energy-rich diet, and carbohydrate-free, cellulose-diluted, low-energy density diet. As a result, after NA injections, rats fed the low caloric diet ingested half as much energy as those fed the high caloric diet (cf. Figs 3 and 4).

An additional phenomenon was also observed. In direct opposition to the NA-induced intake, vehicle injections did stimulate a 1-hour intake in an appropriate manner (i.e. larger intake of the energy diluted diet and smaller intake of the energy rich diet; as if the 1-hour meals were part of a normal daily intake; Fig. 3,

columns on the left). It is important to observe that neither lack of carbohydrates nor low energy density prevented this vehicle infusion-stimulated feeding response (in contrast to the exogenous NA stimulation) to be physiologically meaningful: an appropriate amount of energy rather than food mass was ingested. The results do not support the argument that NA administration specifically induces the intake of diets containing carbohydrates (Leibowitz et al. 1985), since the NA-stimulated intake (mass, not energy) of the HC diet containing carbohydrates was not higher than the consumption of the LP, carbohydrate-free diet.

The rats treated with NA appeared indifferent to the carbohydrate and energy content of the diets and tended to ingest the same food mass, rather than the same amount of metabolizable energy. It seems that neither palatability (high-fiber diets are considered less palatable) nor diet composition were factors preventing a higher than observed intake of the LP diet. To rule out the possible restriction to food intake caused by gastric repletion, we have observed previously that 2-hour intake by a rat could be as high as 16 g of the UAR/A04 chow (Swiergiel and Cabanac 1989). Rather, animals easily habituated to both diets and adjusted their daily intake in accordance with caloric density of the available food.

One of the well-studied adaptive feeding responses in rats is the almost perfect adjustment of energy intake regardless of energy content and density of their diet (Le Magnen 1985). Compensatory changes in caloric intake allow the animals to ingest on a daily basis a consistent amount of energy. This adjustment to a change in the caloric density of a diet, often referred to as "caloric regulation", is one of the cornerstones of all current models of feeding that are linked with the concept of homeostasis (Jacobs and Sharma 1969, Mayer 1967). However, neural mechanisms underlying "caloric regulation" have not yet been determined. A role has been suggested for the PVN-NA system (Leibowitz 1986) but the physiological significance of NA-stimulated feeding relative to the normal day-to-day control of energy intake is still unclear. In our previous study, when wooden pellets were substituted for food, NA infusions still produced vigorous chewing of these inedible objects (Swiergiel and Peters 1987). Therefore, an NA-induced high intake of the low energy diet by rats may be linked to general behavioral arousal, as suggested previously (Swiergiel and Peters 1987) and discussed below.

As a matter of fact, the presented findings are not unexpected, and they do contradict the PVN-NA role in feeding. The caloric homeostasis, confirmed in the present study, is the maintenance of a balance between energy intake and energy expenditure. However, feeding behavior in satiated, non food-deprived rats does not reflect a true need for metabolic fuel, as the animals still have plenty of deposited energy (e.g. fat). Hunger emerges only when there is a change in the predominant source of metabolic fuels from easily available sources (food in the gastrointestinal tract, body carbohydrates) to endogenous body stores. Also, it is important to remember that there are other factors affecting ingestion that have little or nothing to do with caloric homeostasis, for example, palatability (Le Magnen 1985). The mechanisms for controlling feeding can be quite different from those that maintain caloric homeostasis.

The present study aimed to more precisely determine the physiological function of the PVN-NE system in the control of feeding. It was investigated whether the stimulation of hypothalamic PVN by means of NA infusion produced the intake of a given amount of food (expressed as weight or volume of food), or of a certain amount of metabolizable energy. It was found that NA administration increased food intake, not specific to its carbohydrate or energy content. There is a possibility, though we consider it rather unlikely, that food must contain at least some carbohydrates for NA to stimulate a high intake of the low energy density diet.

Therefore, the high intake of the low energy diet by rats suggests that NA-induced ingestion may be linked to general behavioral arousal, as previously suggested (Swiergiel and Peters 1987). This experiment demonstrated that continuous NA infusion changed the pattern of behavior leading to non-nutritive cork chewing episodes and disturbed cage exploration. These results may be considered as additional evidence that NA itself could induce general behavioral response (Zagrodzka et al. 1994, Tanaka et al. 2000) or short lasting motivational activation (Mason 1979, Mason and Iversen 1979, Oades 1985). Such an arousal state under appropriate circumstances, could lead to feeding-like responses which are not necessary directed to the intake of specific food components, for example, carbohydrates. Based on the postulates of Valenstein and his colleagues (1970), and Haller and his group (1998), it seems possible that hypothalamic areas do not play a key role in the creation of basic drives like hunger. Hypothalamic areas are rather responsible for creation of appropriate conditions, or sensitization of the triggering mechanisms. These created conditions are probably involved in the controlling and/or inducing of the well-characterized patterns of an animal's attention-oriented behavioral activity (Valenstein et al. 1969, 1970, Haller et al. 1998). On the other hand, according to Kruk and his colleagues (1998), hypothalamic responses should be considered a fragment of consummatory reactions. The sensory or interoceptive signals that are incorporated in, for example, energy state control, ingestion or drinking, after reaching the hypothalamus (initiation and procurement phases of those behavior), are subsequently transferred to these brain substrates that control the consummatory component of such particular behavioral responses (Swanson and Mogenson 1981, Chen et al. 2001). Thus, as it was mentioned by Kruk and his colleagues (1998), the hypothalamus can be used by animals as "tools in a tool box" whenever such patterns of behavior can be advantageous.

CONCLUSIONS

The results do not support the hypothesis that the noradrenergic system of the PVN that mediates NA feeding response is directly involved in the control of energy intake. Rather, NA may stimulate or gate preprogrammed behaviors that meet the increased demand for energy by facilitating the approach to food and water, and the acquisition and consumption of foods. NA enables these coping behaviors by increased vigilance, activity, and excitability, as well as sensitivity to stimuli and a changed metabolic rate. Our data suggest that increased feeding evoked by NA is related to increased general arousal or the facilitation of oral responses and an augmentation of ingestive behavior in the presence of any kind of edible matter.

ACKNOWLEDGEMENTS

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