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A STUDY OF ACTION OF NOREPINEPHRINE ON HYPOTHALAMIC FEEDING CENTRES

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Abstract : Effects of intrahypothalamic and intraventricular microinjections of norepinephrine (NE) were studied in fasted albino rats. Applications of NE into ventromedial hypothalamus (VMH), medial part of lateral hypothalamus (LH) and lateral ventricle (LV) caused marked but short lasting decrease in food intake, whereas lateral part of LH was insensitive to NE administration. Decrease in water intake seemed secondary to decrease in food intake. Decrease in food intake could not be attributed to the alteration of body temperature. This study explains the mechanism of anorexigenic action of amphetamine and the mechanism of hyperphagia following destruction of the ventral noradrenergic bundle.

Key words : nor-epinephrine hypothalamus food intake water intake body temperature

INTRODUCTION

Experimental studies over the past several decades have indicated the central action of norepinephrine (NE) on food intake which has extensively been reviewed by Leibowitz (1). Evidences for and against the role of NE as an inhibitory transmitter for the control of food intake have been provided in the literature. Grossman (2,3) observed that the administration of NE into LH stimulated food intake in the rat. Leibowitz (4,5) demonstrated that noradrenergic stimulation of food intake occured primarily in the paraventricular nucleus (PVN), whereas LH was insensitive to the application of NE (6). However application of NE on VMH increased food intake (6). If NE is excitatory transmitter in the control of food intake as suggested by Grossman (2,3) and Leibowitz (4,5), experimental procedures which deplete brain NE or block NE transmission should produce aphagia. Destruction of ventral NE bundle caused severe NE depletion and hyperphagia (7). Injection of chlorpromazine which blocks adrenergic transmission in the hypothalamus of satiated rats stimulated feeding (8). Coons and Quartermain (9) reported that rats did not work for food by bar-pressing after the application of NE into the hypothalamus. Thus, they observed motivational depression associated with NE induced eating from the hypothalamus. Margules (10,11,12) reported that application of NE into the perifornical hypothalamus caused suppression of feeding. The central role of NE in the control of food intake is therefore controversial.

Moreover most of the previous experiments were carried out mainly to find out the central action of NE on LH and PVN (1). There is hardly any data (except few e.g.6) about the central action of NE on VMH which ultimately determines the activity of feeding centre (13). Fall in body temperature after microinjection of NE into the hypothalamus itself can modify food intake according to thermostatic theory of Brobeck (13). Evidences have been presented about the inhibitory effect of intrahypothalamic injection of NE on drinking behavior (2,14, 15) which also can alter the feeding behavior (13). This study has been, therefore, undertaken to elucidate the role of NE as a central neurotransmitter concerned with the regulation of food intake and also to explore the relationship of food intake with water intake and body temperature after intrahypothalamic or intraventricular microinjection of N.E.

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METHODS

Male albino Wistar rats (body weight 200-250 gm) were housed in separate cages and maintained on commercial food pellets and water *ad-libitum*. After the animals had adapted themselves to the laboratory conditions, food consumption was measured at intervals of 2 hr for six hr from 10.00 hr to 16.00 hr after an overnight fast. Their daily water intake was also noted. After their daily food intake had been stabilised under the feeding schedule, the animals were considered fit for implantation of cannulae. A fixed length of 15 mm was cut from stainless steel needle of 21 gauge and used as outer cannula. A 27 gauge butterfly connected to 2 microlitre syringe through a fine polythene tubing was used as the inner cannula to inject the solution. 27 gauge needle of 17 mm length was inserted into the outer cannula so that it protruded 2 mm beyond the outer cannula. The cannulae with the stilletes were implanted in the desired areas stereotaxically (INCO), under ether anaesthesia and were fixed with dental cement. The co-ordinates of VMH, LH and LV were derived from the stereotaxic atlas (16). The tip of the cannula was placed 2 mm above the desired hypothalamic area. Experiments were conducted after one week post-operative recovery when their food intake also stabilised. The food and water intake were measured before and after saline (2 µl) and NE injection (2 µg). Rectal temperature was also measured after injection for a period of 6 hr at intervals of half an hour. The site of cannula placement was confirmed later histologically (Fig.1).

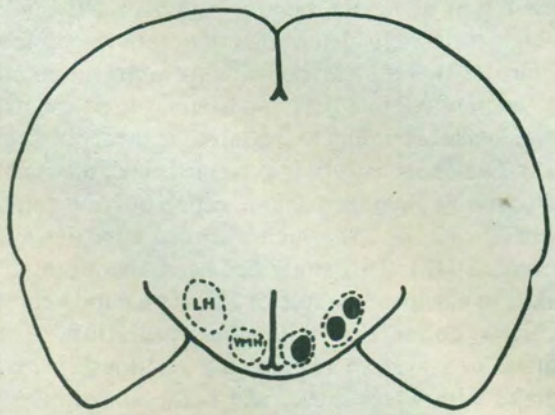

Fig. 1: Section of the brain showing the position of cannulae (shaded areas) in VMH and LH. VMH (2.8 mm behind the bregma, L = 0.5 mm, V = 8.5 mm). LH (2.8 mm behind the bregma, L = 2 mm, V = 8.0 mm).

RESULTS

Effect of microinjection of NE into VMH : There was a significant reduction in food intake throughout the period of observation (2-6 hr) after injection of NE in VMH, as compared to saline. The reduction in food intake was highly significant during the second hour after NE injection. Food intake became normal next day (Fig.2). Water intake remained unaltered, although there was a tendency to drink less water (Fig.2).

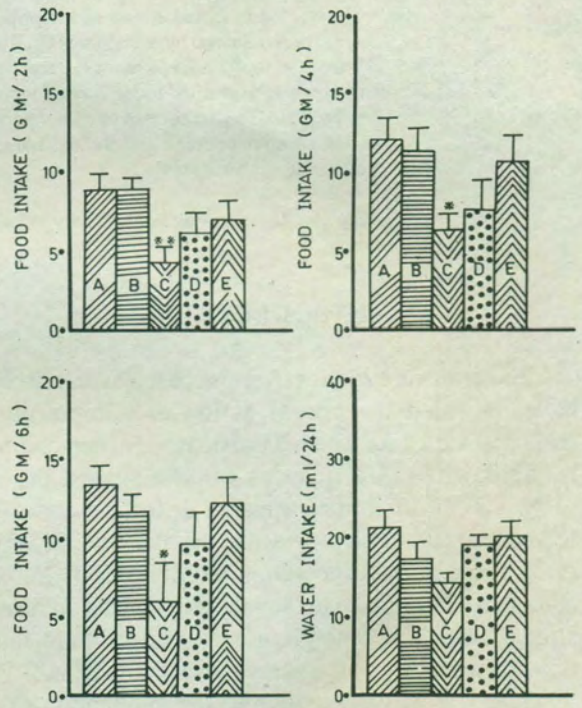

Fig.2: Food intake (Mean ± SE) during the first two hours (top left), four hours (top right) and six hours (bottom left) following microinjection of NE into VMH. Bottom right showing water intake (Mean ± SE) following microinjection of NE into VMH. 'A' = Food/water intake before saline treatment. 'B' = Food/water intake after saline treatment. 'C' = Food/water intake after NE microinjection. 'D' = Food/water intake one day after NE microinjection. 'E' = Food/water intake two days after NE microinjection. * = 'P' value < 0.05, **= 'P' value < 0.01, n = 6.

There was a progressive fall in body temperature upto $1\frac{1}{2}$ hr after NE injection when a peak effect was observed. The temperature gradually approached towards normal after 6 hr (Fig. 3).

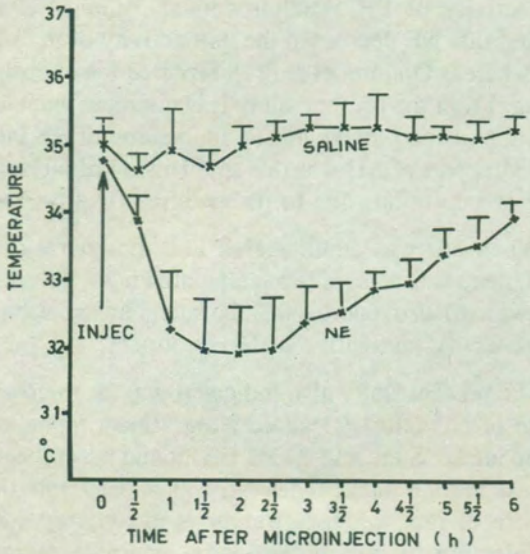

Fig. 3: Rectal temperature (Mean ± SE) following microinjection of saline and NE into VMH, n = 5.

Effect of microinjection of NE into LH (medial part) : There was a significant reduction in food intake without any significant change in water intake after NE microinjection (Fig. 4).

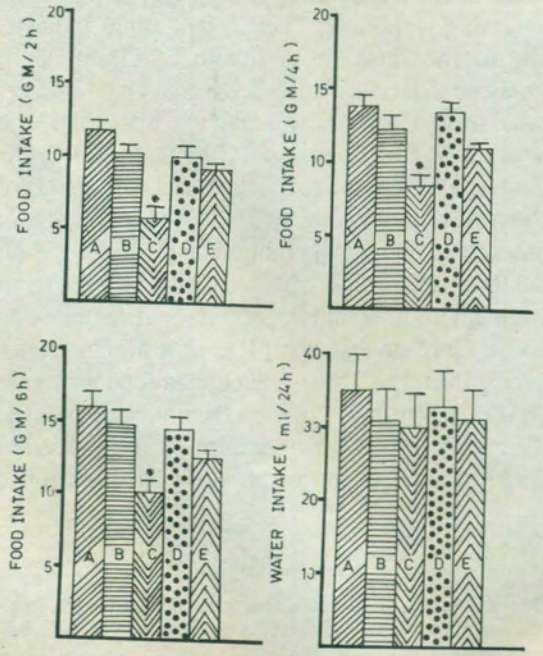

Fig. 4: Food and water intake following microinjection of NE into LH (medial part), n = 4. Rest of the legend is same as in Fig. 2.

Effect of microinjection of NE into LH (lateral part) : There was no significant change in food and water intake after NE microinjection (Fig.5).

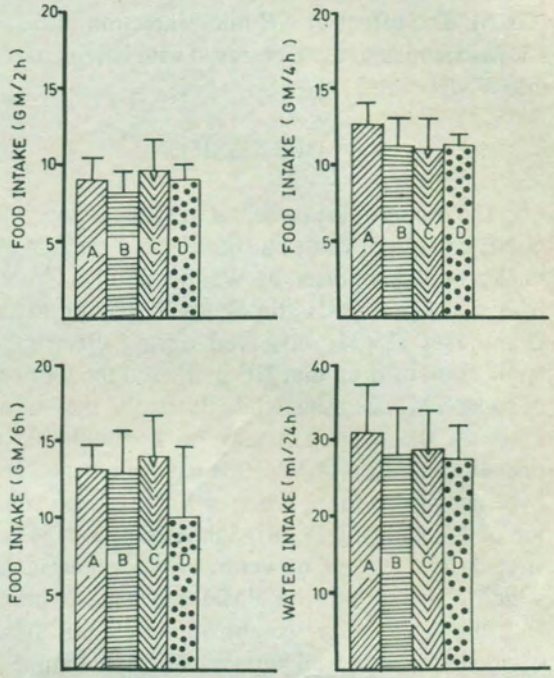

Fig 5: Food and water intake following microinjection of NE into LH (lateral part), n = 3. Rest of the legend is same as in Fig. 2.

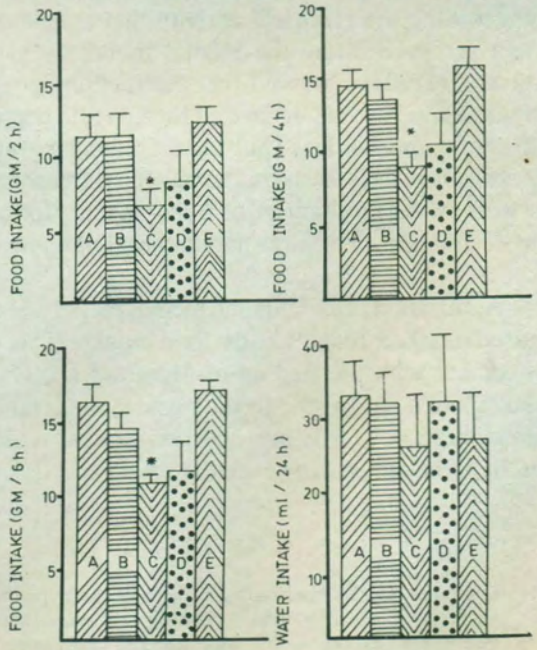

Fig.6: Food and water intake following microinjection of NE into LV. n = 4. Rest of the legend is same as in Fig.2.

Effect of microinjection of NE into LV: There was a significant decrease in food intake and an insignificant reduction in water intake after microinjection of NE (Fig.6). The effect of NE microinjection into LH and LV were similar to those observed with NE microinjection into VMH (Fig.3).

DISCUSSION

The results of the present study suggest that injection of NE into VMH causes a significant reduction in food intake, as also reported by Wagner and De Groot (17). Injected NE in VMH stimulates it, leading to satiety. Oomura et al (21) observed during electrophoretic application of drug that NE increased the unit activity of some VMH neurons while decreased that of others. Probably the net result may be a stimulation rather than an inhibition of VMH. It has been suggested that hyperphagia due to the lesion of VMH is due to destruction of NE pathway (7,18). Sahakian et al (19) demonstrated that lession of ventral noradrenergic bundle which projects into the VMH produced hyperphagia and enhanced body weight, although this has been debated (20). It is well known that amphetamine which reduces food intake liberates NE into the central nervous system. It has been suggested by Brobeck et al (22) by recording the electrical activity that amphetamine could act by exciting the medial inhibitory system. Ahlskog (7) also observed that destruction of ventral noradrenergic bundle decreased the appetite depresant effect of amphetamine. Thus the present study favours the above view about the mechanism of action of amphetamine as well as the mechanism of hyperphagia following the destruction of ventral noradrenergic bundle.

Application of NE into the medial part of LH again caused marked reduction of food intake. This is in agreement with the finding of Mergules (10, 11, 12) who reported suppressed feeding behaviour in rats after administration of NE into the perifornical region of the hypothalamus. However the effect of NE on the Unit activity of LH is controversial. Bloom et al reported that NE decreased the unit activity of the LH (10), whereas Oomura et al (21) reported the opposite finding. From the present study it is not clear whether inhibition of food intake due to application of NE into the medial part of LH was due to diffusion of NE into VMH or inhibition due to its specific effect on LH.

When NE was administered into the lateral part of LH, there was no significant alteration in food intake. Leibowitz (6) also reported that the lateral hypothalamus was generally insensitive to NE treatment.

The present study also indicated that the microinjection of NE into LV caused a significant reduction of food intake. Stern and Zwick (23) found a significant decrease in food intake when NE was injected into the ventricle of rats, whereas Berger et al (24) reported that injection of NE in the lateral ventricle of rats recovering from lateral hypothalamic anorexia increased food intake. The present study also supports the previous contention about the presence of two opposing effects of NE on feeding viz a facilitatory effect via PVN (4,5) and an inhibitory role via VMH or mid lateral hypothalamus at the level of VMH. It appears that diffusion of NE from the lateral ventricle to different areas of the hypothalamus may play an important role in eating responses. The present study indicated that the balance may be in favour of inhibition. In this study no strict correlation between food and water intake was seen. However, a small post-prandial effect on water intake was observed. Hypothermia was the usual finding after NE microinjection. According to Brobeck's "thermostatic hypothesis" (13), the regulation of food intake and body temperature is inter-related. Reduction of food intake was observed due to the exposure to high environmental temperature and satiety was found to be more or less complete at a higher temperature producing fever. Thus, reduction in food intake observed in the present investigation cannot be attributed to the alteration in body temperature by following an intra-hypothalamic or intraventricular NE injection.

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