MODULATION OF FEEDING AND DRINKING BEHAVIOUR BY CATECHOLAMINES INJECTED INTO NUCLEUS ACCUMBENS IN RATS

PRAVATI PAL, SELVAM SRI RAMCHANDRA RAJ, MADAN MOHAN AND G. K. PAL*

Department of Physiology,
Jawaharlal Institute of Postgraduate Medical Education and Research,
Pondicherry – 605 006

Abstract : Nucleus accumbens is proposed as one of the centers in the neural circuitry involved in the regulation of feeding and drinking behaviour in rats. Injection of dopamine and angiotensin-II into this nucleus has been documented to affect water and food intake in rats. Reports on the effect of intracerebral injection of catecholamines on feeding and drinking behaviour in animal models are conflicting. Therefore, in the present study the effect of adrenaline and noradrenaline injected into nucleus accumbens on food and water intake in rats was assessed. 24 h basal food and water intakes were recorded in Wistar rats and were found to be 12.3 ± 0.46 g and 21.7 ± 1.03 ml respectively. Stainless steel cannulae were implanted stereotaxically into the nucleus accumbens. Four different doses (0.1 µg, 0.5 µg, 1 µg, and 2 µg) of adrenaline and noradrenaline were injected into the nucleus accumbens through the implanted cannulae in different group of animals and their 24 h food and water intakes were recorded following these injections. No change in food and water intake was observed following the administration of different doses of adrenaline. A significant increase in 24 h water intake reaching a maximum of 28.88 ± 1.45 ml at 1 µg dose, without change in food intake was observed following administration of different doses of noradrenaline. The noradrenaline-facilitated water intake was blocked when noradrenaline was injected following injection of phentolamine, an α-receptor blocker. The bilateral lesions of nucleus accumbens resulted in a significant and sustained inhibition of water intake (16.61 ± 0.67 ml) without change in food intake. These observations suggest that noradrenaline facilitates water intake without affecting food intake when injected into the nucleus accumbens in rats and the dipsogenic effect of noradrenaline is mediated by α-receptors. Adrenaline does not affect these ingestive behaviours when injected into the nucleus accumbens in rats.

Key words : nucleus accumbens   food intake   water intake
               adrenaline   noradrenaline   phentolamine

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*Corresponding Author

INTRODUCTION

Catecholamines have long been implicated in modulation of food and water intake (1–3). Earlier it has been reported that peripheral and intracerebral administration of α-receptor agonists decrease drinking (4–6) whereas β-receptor agonists increase drinking (7, 8). Moreover, α-receptor antagonists increase whereas β-receptor antagonists decrease drinking whether injected peripherally or intracerebrally (9, 10). However, reports of recent studies on the role of α and β-receptors on food and water intake in animal models are conflicting (11–13). Adrenaline decreases food intake when injected intraperitoneally but increases food intake when injected intracerebrally (14–16). In a recent review it has been reported that noradrenaline injected intracerebrally inhibits fluid intake but it either stimulates or does not change food intake (17). But, reports also suggest that noradrenaline facilitates water intake and food intake when injected intracerebrally either into lateral ventricle or into other areas of the brain (18, 19). Other studies have also revealed the conflicting nature of the involvement of catecholamines in the modulation of feeding and drinking behaviours in rats (20–24). According to these studies adrenaline increases food intake by increasing bar pressing when animal is exposed to scheduled-food intake (20), noradrenaline inhibits food intake (21, 22), and adrenaline also inhibits food intake (23, 24). Therefore, it is clear that the reports on the role of catecholamines on food and water intake are contradictory.

Nucleus accumbens has been reported to be involved in the regulation of food and water intake in rats (25, 26). In an earlier work from our laboratory, it was reported that injection of dopamine into nucleus accumbens facilitates water intake in a dose dependent manner (27). It was also reported that dopamine-faciliated water intake is independent of food intake (28). No work has been done yet to study the effects of noradrenaline and adrenaline injected into the nucleus accumbens on food and water intake in animal models. Therefore, the present study was carried out to assess the effect of adrenaline and noradrenaline injected into the nucleus accumbens on food and water intakes in rats. The study was also designed to clarify the conflicting reports of the involvement of catecholamines and their receptors on food and water intake in rats.

METHODS

Institute bred 50 albino rats of Wistar strain with body weights of 200 to 300 g were used for this study. Each animal was kept in a separate cage. The temperature of the room in which animals were caged was between 25 to 28°C. Animals were exposed to 24 h natural light-dark cycle. Food and water were provided *ad lib*.

Basal food and water intake measurement

The food and water were provided at 14.00 h every day following which 24 h food and water intakes were measured for each animal. For water intake, the tap water at room temperature (28°C) was provided in a calibrated glass cylinder with a sprout. The measuring cylinder had the provision of

measuring water intake upto a minimum of 0.5 ml. The food was given in the form of standard rodent chow (food pellets). The food intake was measured by taking the weight of the food in the electronic weighing machine. The food was placed in the space for food provided in the cage. The weight of the food was taken before placing the food in the cage and the weight of the food was again measured after 24 h by collecting the remaining of the food from the cage. The difference between these two weights was taken as the 24 h food intake. Daily food and water intakes were recorded for 7 consecutive days to determine the 24 h basal mean food and intake of each animal.

Cannulations

Stainless steel cannulae of desired length were prepared by appropriately cutting the 24 G needles. The cannulae were implanted unilaterally on the right side in 40 animals into nucleus accumbens by stereotaxy using the coordinates of Konig and Klippel (29). The coordinates for nucleus accumbens were: anterior-10 mm, lateral-1.2 mm, horizontal-0.4 mm. Sterotaxic surgery was performed aseptically under chloralose anesthesia (100 mg/kg, i.p.; S.D. Fine-Chem. Ltd., Boisar, Maharashtra) supplemented by anesthetic ether (Vitramika Pharma Pvt. Ltd., Nadiad, Gujrat) whenever needed. After surgery, animals were allowed 1 week for full recovery before the different experiments were performed.

Preparation of dosages of chemicals

Four different strengths of stock solutions of adrenaline, noradrenaline, and phentolamine (N.I. Pharma, Calcutta) were prepared separately by proportionately dissolving the chemicals in normal saline in such a way that 1 µl of each solution contained either of the four different doses (0.1, 0.5, 1, and 2 µg, each dose dissolved in 1 µl of normal saline) of the chemicals. The stock solutions were preserved in the refrigerator. However, the temperature of chemicals was brought to the room temperature prior to injection into the nucleus. The solutions containing the chemicals were isotonic.

Experiments performed

The following 4 experiments were carried out in different group of animals.

Experiment 1 :

16 animals were taken for this experiment and were equally divided into 2 groups: the experimental group, and the control group. In the experimental group of 8 animals, 4 different doses (0.1, 0.5, 2, and 2 µg; each dose dissolved in 1 µl of normal saline) of adrenaline were injected separately every day into the nucleus accumbens through the implanted cannulae at 14.00 h following which 24 h food and water intakes were recorded. Each dose of the chemical was injected slowly from a microliter syringe (Top S. M. Co., Bombay) fitted into a Continuous Slow Injector (INCO), over a period of 10 minutes. Adrenaline doses were injected randomly to the animals in such a way that all the animals received all 4 doses of adrenaline on different days. The interval between administration of 2 different doses of the chemical was 24 h. In control group of 8 animals the equal volume (1 µl) of

normal saline without chemical was injected into the nucleus following which 24 h food and water intakes were recorded.

Experiment 2 :

In the experimental group of 8 animals, 4 different doses (0.1, 0.5, 1, and 2 µg; each dose dissolved in 1 µl of normal saline) of noradrenaline were injected in a similar way (as described in Expt. 1) into the nucleus accumbens every day at 14.00 h following which 24 h food and water intakes were recorded. The noradrenaline doses were given separately and randomly to all the animals in such a way that each animal received all the doses of the chemical on different days. The control group of 8 animals received equal volume of normal saline without noradrenaline.

Experiment 3 :

As the maximum change in water intake was observed at injection of 1 µg dose of noradrenaline (in Expt 2), 24 h food and water intakes were recorded in another group of 8 animals after injection of the same dose (1 µg/1 µl) of noradrenaline immediately following the injection of equal dose (1 µg/1 µl) of phentolamine, an α receptor blocker, into the nucleus accumbens. 24 h food and water intakes were also recorded following injection of phentolamine (1 µg/1 µl) alone into the nucleus accumbens.

Experiment 4 :

8 animals were taken for this experiment. Stainless steel electrodes were prepared and insulated (except the tip of the electrodes) by perspex material dissolved in chloroform. the electrodes were implanted bilaterally into the nucleus accumbens in all the animals by stereotaxy. The electrolytic lesions of the nuclei were produced by passing an anodal current of 2 mA for 15 seconds with the help of a lesion maker (INCO). After a recovery period of 1 week food and water intakes were recorded for 7 consecutive days in all animals to record the mean post-lesion food and water intake. The food and water intake of the post-lesion period was compared with their pre-lesion values.

Confirmation of cannulations and site of lesions

After completion of experiments all the animals were sacrificed and their brains were fixed after intracardiac perfusion of 0.9% saline followed by 10% formalin. Brains were removed and placed in 10% formalin for 5 days and were then embedded in paraffin. Sections of the brain of 5 µ thickness were cut with the help of a microtome (ERMA, Japan) and were stained with hematoxylin and eosin. Stained brain sections were fixed on the slides and the site of cannulations and lesions were confirmed by microscopic examination of the sections.

Statistical analysis was done by Student's 't' test.

RESULTS

The mean basal food and water intakes of all the animals were found to be 12.88 ± 0.52 g and 21.81 ± 1.18 ml respectively.

Cannulae and lesion localization

The histological analysis revealed the accuracy of cannulations and lesions (Fig. 1).
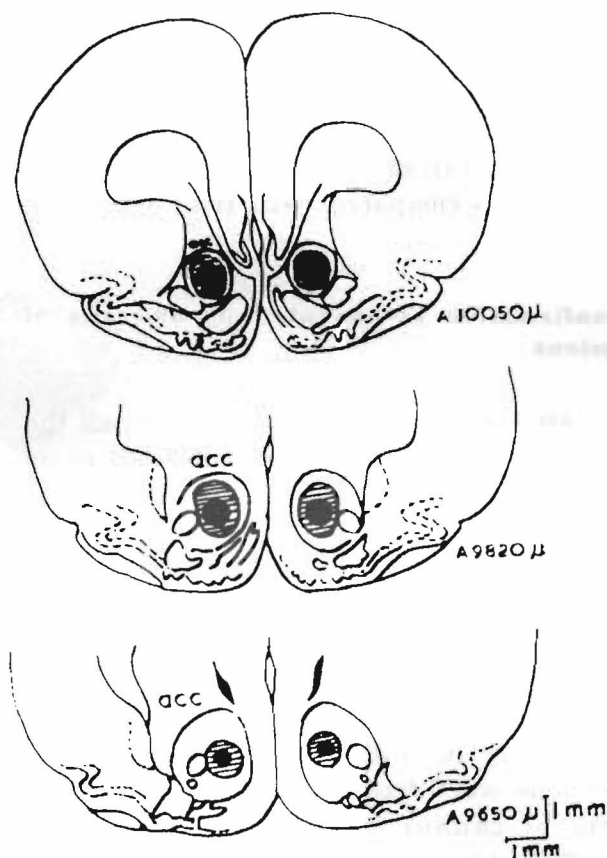

Fig. 1 Reconstruction diagram of rat brain sections: The striped area in the nuclei on both the sides represents the maximum extent of lesions; the darkened area in the nucleus of the right side represents the area to which tip of cannulae were confined; acc = Nucleus Accumbens.

Experiment 1 :

The mean basal food and water intakes were 12.31 ± 0.46 g and 21.69 ± 1.03 ml respectively in experimental animals and 12.75 ± 0.65 g and 22.62 ± 1.01 ml respectively in control animals. There was no significant change observed in food and water intake following administration of different doses of adrenaline into nucleus accumbens in experimental animals (Table I). The food and water intake also remained unchanged in control animals.

TABLE I : Change in 24 h food intake (FI) and water intake (WI) following injection of different doses of adrenaline (Ad) into nucleus accumbens in rats.

Ad doses (μg)	FI (g) Mean±S.D.±S.E.	WI (ml) Mean ± S.D. ± S.E
0.0 (Basal)*	12.31±1.31±0.46	21.69±2.91±1.03
0.1	12.62±1.43±0.51	22.19±2.78±0.98
0.5	12.88±1.48±0.52	22.19±2.98±0.05
1.0	12.75±1.83±0.65	22.62±2.86±1.01
2.0	12.63±1.73±0.61	22.38±2.92±1.03

*Basal means the basal 24 h FI and WI of animals before injection of different doses of Ad.

Expriment 2 :

The mean basal food and water intakes were 12.45± 0.40 g and 20.69 ± 0.82 ml respectively in experimental animals and 12.69 ± 0.47 g and 21.39 ± 0.22 ml respectively in control animals. There was no significant change in food intake observed following administration of different doses of noradrenaline into the nucleus accumbens (Table II). No significant change in water intake was observed following injection of 0.1 μg dose of noradrenaline. A significant and dose dependent increase in water intake without change in food intake was observed following intracerebral injection of 0.5 μg, 1 μg, and 2 μg dose of noradrenaline into the nucleus accumbens. The maximum increase in water intake (28.56 ± 1.39 ml) was observed at 1 μg dose of noradrenaline. However, no further significant increase in water intake was observed following injection of 2 μg dose of noradrenaline

as compared with the result of 1 µg dose of the chemical. The food and water intake remained unchanged in control animals.

TABLE II : Change in 24 h food intake (FI) and water intake (WI) following injection of different doses of noradrenaline (NA) into nucleus accumbens in rats.

NA doses (µg)	FI (g) Mean±S.D.±S.E.	WI (ml) Mean ± S.D. ± S.E
0.0 (Basal)#	12.45±1.41±0.40	20.59±2.33±0.82
0.1	12.88±1.48±0.52	21.18±3.34±1.18
0.5	12.75±1.34±0.47	25.88±3.93±1.39**
1.0	12.75±0.96±0.34	28.56±3.90±1.38***
2.0	12.69±1.33±0.47	28.88±4.11±1.45***

**$P<0.01$, *** $P<0.001$; # Basal means the basal 24 h FI and WI of animals before injection of different doses of NA.

Experiment 3 :

A significant rise in water intake (28.69 ± 0.50 ml) without change in food intake was observed following administration of 1 µg dose of noradrenaline into the nucleus accumbens (Table III). This noradrenaline-facilitated water intake was blocked (water intake was almost decreased to the basal level) when 1 µg of noradrenaline was injected immediately following

TABLE III : Change in 24 h food intake (FI) and water intake (WI) following injection of different doses of noradrenaline (NA) and phentolamine (PL) into nucleus accumbens in rats.

Doses (µg)	FI (g) Mean±S.D.±S.E.	WI (ml) Mean ± S.D. ± S.E
Zero dose (Basal)#	12.25±0.93±0.33	21.13±1.75±0.62
NA (1µg) alone	12.63±0.69±0.25	28.69±1.41±0.50***
PL (1µg)+NA (1µg)	12.25±0.80±0.28	21.56±1.32±0.47
PL (1µg) alone	12.00±0.76±0.27	18.00±1.81±0.64***

**$P<0.01$, *** $P<0.001$; # Basal means the basal 24 h FI and WI of animals before injection of different doses of NA.

the injection of equal dose of phentolamine (1 µg). The water intake was suppressed significantly to 18 ± 0.64 ml from the basal value of 21.13 ± 0.62 ml following injection of phentolamine (1 µg) alone into the nucleus accumbens.

Experiment 4 :

A sustained and significant decrease in water intake was observed following bilateral electrolytic lesions of nucleus accumbens (Table IV). The water intake was suppressed from the basal value of 22.91 ± 0.91 ml to 16.61 ± 0.67 ml. But there was no significant change observed in food intake following the lesions of the nucleus accumbens.

TABLE IV : Change in 24 h food intake (FI) and water intake (WI) following bilateral electrolytic lesion of nucleus accumbens in rats.

	FI (g) Mean ± S.D. ± S.E.	WI (ml) Mean ± S.D. ± S.E
Before lesion	13.89±0.94±0.35	22.91±0.41±0.91
After lesion	13.73±0.73±0.27	16.61±1.79±0.67***

*** $P<0.001$

DISCUSSION

Adrenaline and noradrenaline are neurotransmitters present in the central nervous system, which are related to the control of ingestive behaviour of food and fluid (1–10). Several ways of inducing water intake such as water deprivation, meal associated water intake, administration of dipsogenic chemicals or hyperosmotic solutions, etc. has been reported to be inhibited by α adrenergic agonists and facilitated by β receptor agonists (4–8). It has also been suggested that integrity of central noradrenergic system is necessary for normal expression of water or salt intake

in dehydrated animals and also angiotensinergic component of drinking behaviour apparently depends on an intact central noradrenergic system (14). It has been observed that feeding increases the release of catecholamines in hypothalamus and in mesolimbic areas (30–36). It has also been seen that noradrenaline increases feeding but not drinking when injected into lateral ventricle or hypothalamus (19, 37), whereas adrenaline decreases both food and water intake (16).

In our present study we observed that food and water intake remained unchanged when adrenaline was injected into nucleus accumbens, but a significant and dose-dependent increase in water intake without change in food intake occurred following administration of noradrenaline into the same nucleus. This indicates that noradrenaline is a possible dispsogenic neurotransmitter in nucleus accumbens and the dipsogenic action of noradrenaline is independent of food intake. Facilitation of water intake without change in food intake suggests that this type of polydipsia may be a primary polydipsia as food has not affected the dipsogenesis. Increase in water intake following administration of noradrenaline was observed in a dose-dependent manner. The maximum increase in water intake was observed at 1 μg dose of noradrenaline. No further increase in water intake was observed following increase in the dose of noradrenaline from 1 μg to 2 μg, which may possibly due to receptor saturation. That means the receptors that are available for stimulation of water intake were fully occupied at 1 μg dose of noradrenaline. Therefore, with further increase in the dose of noradrenaline no further increase in

water intake was observed. The mechanism of modulation of food and water intake by catecholamines is not clearly understood. But, it has been proposed that noradrenaline facilitates water intake by acting on post-synaptic receptors (14). In the present study, we observed that water intake facilitated by noradrenaline was blocked when noradrenaline was injected immediately following the injection of phentolamine, an α receptor antagonist. This indicates that noradrenaline-facilitated water intake was mediated by α receptor as phentolamine prevented noradrenaline-induced dipsogenesis. There are two types of α receptors: α_1 and α_2. Phentolamine is a nonspecific α receptor blocker which blocks α_1 and α_2 receptors equally. Therefore, it needs further investigation to identify the type of α receptors involved in elicitation of noradrenaline-induced water intake.

Sustained and significant decrease in 24 h water intake without change in food intake following bilateral lesions of nucleus accumbens indicates that this nucleus has a stimulatory effect on water intake. This result is consistent with the report of our earlier study (27, 28) that administration of dopamine into nucleus accumbens increases water intake. Facilitation of drinking by administration of noradrenaline into the same nucleus further proves that the nucleus accumbens is one of the dipsogenic nuclei and catecholamines are among the dipsogenic neurotransmitters in rats.

Food intake is closely associated with water intake. Increase in food intake usually results in increased water intake primarily by changing the plasma osmolality. This type of facilitation of water intake is known as

postprandial dipsogenesis (38–40). Therefore, whenever research experiments related to water intake are performed food intake is usually studied simultaneously to see whether the change in water intake is influenced by food intake. As in our study change in water intake following intracerebral injection of noradrenaline into the nucleus accumbens or electrolytic lesion of nucleus accumbens was not associated with change in food intake, it can be concluded that this noradrenaline-facilitated water intake is a true polydipsia.

CONCLUSION

We conclude that nucleus accumbens is a facilitatory dipsogenic nucleus in rats and noradrenaline is one of the dipsogenic neurotransmitters in this nucleus. The noradrenaline-facilitated water intake is mediated by α receptors. Water intake induced by noradrenaline injected into nucleus accumbens is independent of food intake. But, evaluation of the involvement of other receptors and receptor subtypes in modulation of water intake by catecholamines injected into nucleus accumbens needs further investigation and research.

ACKNOWLEDGEMENTS

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