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

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(Received on July 7, 2000)

Abstract: Lesions of nucleus caudatus have been documented to produce
adipsia and aphasia in rats. Injection of dopamine into this nucleus has
been shown to facilitate water intake in rats. But, reports are not available
on the effects of intracerebral injection of epinephrine and norepinephrine
on feeding and drinking behaviour in animal models. Therefore, in the
present study the effect of adrenaline and noradrenaline injected into
nucleus caudatus 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 12.37 ± 0.20 g and 22.04 ± 0.27 ml respectively. Stainless steel
cannulae were implanted stereotaxically into the nucleus caudatus. Four
different doses (0.1 µg, 0.5 µg, 1 µg, and 2 µg) of adrenaline and
noradrenaline were injected into the nucleus caudatus through the
implanted cannulae in separate groups 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 food intake reaching a
maximum of 16.03 ± 0.15 g at 2 µg dose, without change in water intake
was observed following administration of different doses of noradrenaline.
The noradrenaline-facilitated food intake was blocked when noradrenaline
was injected following injection of phentolamine, an α-receptor blocker.
The bilateral lesions of nucleus caudatus resulted in a significant and
sustained inhibition of food (8.98 ± 0.17 g) and water intake (19.12 ± 0.16
ml) These observations suggest that nucleus caudatus is involved in
regulation of food and water intakes in rats. Noradrenaline-facilitated
food intake is mediated by α-receptors. Adrenaline does not affect these
ingestive behaviours when injected into the nucleus caudatus in rats.

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

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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 (4-6) whereas β-receptor agonists increase (7, 8) drinking and feeding behaviours. Moreover, β-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 intakes in animal models are conflicting (11-13). Adrenaline decrease 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 food and water 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 caudatus has been reported to be involved in the regulation of food and water intake in rats (25, 26). Bilateral kainic acid lesion of nucleus caudatus has been documented to produce adipsia in cats (27). In an earlier work from our laboratory, it was reported that injection of dopamine into nucleus caudatus facilitates water intake in a dose dependent manner (28) and lesion of caudate nucleus disrupts feeding schedule and food intake in rats (29). It was also reported that dopamine-facilitated water intake is independent of food intake (30). No work has been done yet to study the effects of noradrenaline and adrenaline injected into the nucleus caudatus 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 caudatus on food and water intake in rats. This 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 40 male 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 up to a minimum of 0.5ml. 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 water 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 30 animals into nucleus caudatus by stereotaxy using the coordinates of Konig and Klippel (31). The coordinates for nucleus caudatus were: anterior 7.8 mm, lateral 2.6 mm, and horizontal 0.0 mm. Stereotaxic 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, Gujarat) whenever needed. After surgery, animals were allowed one 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 1µl of normal saline) of the chemicals. The stock solutions were preserved in the refrigerator. However, the temperature of the 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:** 20 animals were taken for this experiment and were equally divided into two groups: the experimental group, and the control group. In the experimental group of 10 animals four different doses (0.1, 0.5, 1, and 2 µg; each dose dissolved in 1µl of normal saline) of adrenaline were injected separately every day into the nucleus caudatus 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 four doses of adrenaline on different days. The interval between administration of two different doses of the chemical was 24 h. In control group of 10 animals the equal volume (1μl) of normal saline without chemical was injected into the nucleus following which 24 h food and water intakes were recorded.

**Experiment 2**: After the completion of experiment 1, the same animals were used for the experiment 2. In the experimental group of 10 animals, four different doses (0.1, 0.5, 1, and 2 μg; each dose dissolved in 1μl of normal saline) of noradrenaline were injected in a similar way (as described in experiment 1) into the nucleus caudatus 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 10 animals received equal volume of normal saline without noradrenaline.

**Experiment 3**: As the maximum change in food intake was observed at injection of 2 μg dose of noradrenaline (in experiment 3), 24 h food and water intakes were recorded in another group of 10 animals after injection of the same dose (2μg/μl) of noradrenaline into the nucleus caudatus immediately following the injection of equal dose (2 μg/μl) of phentolamine, an α receptor blocker. 24 h food and water intakes were also recorded following injection of phentolamine (2μg/μl) alone into the nucleus caudatus.

**Experiment 4**: 10 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 caudatus 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 5 days, food and water intakes were recorded for seven 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 5μ thickness were cut with the help of a microtome (ERMA, Japan) and were stained with hematoxylin and eosin. Stained sections were fixed on the slides and the site of cannulations and lesions were confirmed by microscopic examination.

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 12.49±0.13 g and 22.15±0.17 ml respectively.
Experiment 1: The mean basal food and water intakes were 12.37 ± 0.20 g and 22.04 ± 0.27 ml respectively in experimental animals and 12.58 ± 0.19 g and 22.03 ± 0.21 ml respectively in control animals. There was no significant changes observed in food and water intake following administration of different doses of adrenaline into nucleus caudate in experimental animals (Table I). The food and water intakes also remained unchanged in control animals.

Experiment 2: The mean basal food and water intakes were 12.37 ± 0.20 g and 22.04 ± 0.27 ml respectively in experimental animals and 12.58 ± 0.19 g and 22.03 ± 0.21 ml respectively in control animals. There was no significant change in water intake observed following administration of different doses of noradrenaline into the nucleus caudatus (Table II). No significant change in food intake was observed following injection of 0.1 and 0.5 μg dose of noradrenaline. A significant increase in food intake without change in water intake was observed following intracerebral injection of 1 μg, and 2 μg dose of noradrenaline into the nucleus caudatus. The maximum increase in food intake (16.03 ± 0.15 g) was observed at 2 μg dose of noradrenaline. The food and water intake 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 caudatus in rats of experimental group. |
|---------------------------------|----------------|----------------|
| Ad doses (μg)  | FI (g) Mean ± S.D. ± S.E. | WI (ml) Mean ± S.D. ± S.E. |
| 0.0 (Basal)# | 12.37±0.63±0.20 | 22.04±0.87±0.27 |
| 0.1             | 12.38±0.44±0.14 | 22.08±0.77±0.24 |
| 0.5             | 12.33±0.46±0.14 | 22.18±0.78±0.24 |
| 1.0             | 12.49±0.59±0.18 | 22.13±0.91±0.28 |
| 2.0             | 12.45±0.59±0.18 | 22.26±0.84±0.26 |

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

| TABLE II: Change in 24 h food intake (FI) and water intake (WI) following injection of different doses of noradrenaline (NA) into nucleus caudatus in rats of experimental group. |
|---------------------------------|----------------|----------------|
| NA doses (μg)  | FI (g) Mean ± S.D. ± S.E. | WI (ml) Mean ± S.D. ± S.E. |
| 0.0 (Basal)# | 12.37±0.63±0.20 | 22.04±0.87±0.27 |
| 0.1             | 12.59±0.65±0.20 | 22.15±0.62±0.19 |
| 0.5             | 12.46±0.52±0.16 | 22.94±0.53±0.16 |
| 1.0             | 14.23±0.52±0.16*** | 22.13±0.57±0.18 |
| 2.0             | 16.03±0.50±0.15*** | 22.16±0.41±0.13 |

***P<0.01; #Basal means the basal 24 h FI and WI of animals before injection of different doses of NA.
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 caudatus in rats.

<table>
<thead>
<tr>
<th>Doses (µg)</th>
<th>FI (g) Mean ± S.D. ± S.E.</th>
<th>WI (ml) Mean ± S.D. ± S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero dose (Basal)#</td>
<td>12.42±0.52 ±0.16</td>
<td>21.87±0.65±0.20</td>
</tr>
<tr>
<td>NA (2 µg) alone</td>
<td>16.23±0.56 ±0.17***</td>
<td>21.77±0.48±0.15</td>
</tr>
<tr>
<td>PL (2 µg) + NA (2µg)</td>
<td>12.17±0.65 ±0.20</td>
<td>21.88±0.61±0.19</td>
</tr>
<tr>
<td>PL (2 µg) alone</td>
<td>9.55±0.58 ±0.18***</td>
<td>21.52±0.71±0.22</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>FI (g) Mean ± S.D. ± S.E.</th>
<th>WI (ml) Mean ± S.D. ± S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before lesion</td>
<td>12.68±0.55 ±0.17</td>
<td>22.28±0.77±0.24</td>
</tr>
<tr>
<td>After lesion</td>
<td>8.98±0.56 ±0.17***</td>
<td>19.12±0.53±0.16***</td>
</tr>
</tbody>
</table>

***P<0.001

Experiment 3: A significant rise in food intake (16.23 ± 0.17 g) without change in water intake was observed following administration of 2 µg dose of noradrenaline into the nucleus caudatus (Table III). This noradrenaline-facilitated food intake was blocked (food intake was almost decreased to the basal level) when 2 µg of noradrenaline was injected immediately following the injection of equal dose of phentolamine (2 µg). The food intake was suppressed significantly to 9.55 ± 0.18 g from the basal value of 12.42 ± 0.16 g following injection of phentolamine (2 µg) alone into the nucleus caudatus.

Experiment 4: A sustained and significant decrease in food and water intake was observed following bilateral electrolytic lesions of nucleus caudatus (Table IV). The food intake was suppressed from the basal value of 12.68 ± 0.17 g to 8.98 ± 0.17 g. The water intake was also suppressed from the basal value of 22.28 ml ± 0.24 ml to 19.12 ± 0.16 ml.

DISCUSSION

Sustained and significant decrease in 24 h food and water intakes following bilateral lesions of nucleus caudatus indicates that this nucleus has a stimulatory effect on food and water intake in rats. This result is consistent with the report of our earlier studies that administration of dopamine into nucleus caudatus increases water intake and lesion of caudate nucleus disrupts feeding behaviour (28, 29, 30). Facilitation of food intake by administration of noradrenaline into the same nucleus further establishes that the nucleus caudatus is one of the
Catecholamines are neurotransmitters distributed in various parts of the central nervous system that are related to the control of ingestive behaviour of food and fluid (1-10). It has been observed that feeding increases the release of catecholamines in hypothalamus and in mesolimbic areas (32-38). It has also been seen that noradrenaline increases feeding but not drinking when injected into lateral ventricle or hypothalamus (19, 39), whereas adrenaline decreases both food and water intake (16). Recently it has been observed that hunger increases regional cerebral blood flow in the caudate nucleus (40) and drinking increases release of dopamine in the caudate nucleus (41).

In our present study we observed that food and water intake remained unchanged when adrenaline was injected into nucleus caudatus, but a significant increase in food intake without change in water intake occurred following administration of noradrenaline into the same nucleus. This indicates that noradrenaline is a possible neurotransmitter in nucleus caudatus involved in elicitation of food intake which is independent of water intake. Increase in food intake following administration of noradrenaline was observed only at higher doses of the chemical. The maximum increase in food intake was observed at 2 µg dose of noradrenaline. The mechanism of modulation of food and water intake by catecholamines is not clearly understood. In the present study we observed that food 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 food intake was mediated by α receptors as phentolamine prevented noradrenaline-induced food intake. There are two types of α receptors: α₁ and α₂. Phentolamine is a nonspecific α receptor blocker, which blocks α₁ and α₂ receptors equally. Therefore, it needs further investigation to identify the type of α receptors involved in elicitation of noradrenaline-induced food intake.

Water intake is closely associated with food 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 (42-44). But, in our study increase in food intake following injection of noradrenaline into nucleus caudatus was not associated with significant change in water intake. Though the nucleus caudatus has an excitatory effect on both food and water intakes (as lesion of this nucleus inhibits feeding and drinking), noradrenaline facilitates only the food intake but not the water intake when injected into this nucleus. This proves that noradrenaline is not a dipsogenic neurotransmitter in nucleus caudatus. It needs further investigation to establish why increase in food intake following administration of noradrenaline into nucleus caudatus was not associated with postprandial dipsogenesis.

**CONCLUSION**

We conclude that nucleus caudatus facilitates food and water intakes in rats...
and noradrenaline injected into this nucleus increases food intake. The noradrenaline-facilitated food intake is mediated by α receptors, and this increase in food intake is independent of water intake. But, evaluation of the involvement of other receptors and receptor subtypes in modulation of food intake by catecholamines injected into nucleus needs further investigation and research.

REFERENCES


