THE EFFECT OF SIMULTANEOUS INTRAVENTRICULAR ADMINISTRATION OF NORADRENALINE AND DOPAMINE ON LATERAL HYPOTHALAMIC SYNDROME IN RATS

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Abstract. The effect of intraventricular administration of noradrenaline (NA), dopamine (DA) or both on the lateral hypothalamic (LH) syndrome of aphagia and sensorimotor impairments was studied on 22 male hooded rats. It was found that 120 nmol of NA increased intake of palatable food in LH rats by $29.5 \pm 10.5\%$, 120 nmol of DA by $17.5 \pm 6.5\%$, and 60 nmol of simultaneously given each of catecholamine by $47.0 \pm 15.0\%$. Intraventricular catecholamines also induced the intake of normal food pellets even in completely aphagic rats. On the other hand they did not improve sensorimotor disturbances evoked by LH lesions. It is concluded that lateral hypothalamic aphagia may be attributed to the disruption of NA and DA pathways passing through LH and that these pathways potentiate the action of each other with regard to food intake.

Electrolytic lesions directed to the lateral hypothalamus produce the well known syndrome of aphagia, adipsia and sensorimotor impairments (10, 11, 16). Very similar disturbances were observed after the administration of 6-hydroxydopamine into the cerebral ventricle (18) or to several sites along the nigro-striatal dopaminergic pathways (17). Hypothalamic lesions both electrolytic (1, 7) and chemical (18) have also been reported to cause widespread depletion of brain noradrenaline and dopa-
mine. All these facts suggest that disruption of the ascending catecholaminergic pathways running within the medial forebrain bundle may be responsible for various symptoms seen after the lateral hypothalamic damage (4, 17, 18). If so, one may expect that exogenous NA and DA will mimic the function of the disrupted catecholaminergic systems. The first experiments to test this possibility were performed by Berger et al. (4) who found a temporary reversal of aphagia after NA treatment, and Ungerstedt (17) who observed increased motility after apomorphine in rats with LH damage.

As the lateral hypothalamus carries the fibers of both NA and DA systems and there is evidence that these systems interact with each other in various behavioral functions (see 3, 8), possible consequences of such an interaction for the reversal of the main disturbances after LH lesions were examined in the present paper. For this purpose we compared the effects of simultaneous intraventricular injections of both NA and DA with the effects of each catecholamine given separately to LH—damaged rats.

The experiment was carried out on 22 male hooded rats sham operated or subjected to the bilateral electrolytic lesions of the lateral hypothalamus according to the following coordinates: 2.7 mm posterior to the bregma, 1.3 mm lateral to the midline and 8.9 mm below the skull surface (anodal current of 2 mA for 20 s). All animals were also implanted with unilateral cannulas located within the left lateral ventricle.

Beginning with the second postoperative day the following measurements were performed on each rat: (a) daily food and water intake, (b) body weight, (c) neurological examination of sensorimotor functions, without injections and after intraventricular catecholamines, (d) intake of highly palatable food (a mixture of crushed chocolate cookies and water) in 10-min test, without injections and after intraventricular ones, and (e) intake of normal food pellets in 10-min test, without injections and after catecholamines. The neurological examination was performed according to the description given by Marshall and Teitelbaum (10) and Schallert and Whishaw (14). The animals were subjected to the following tests: (a) orientation to tactile stimulation of vibrissae and body surface, (b) resistance to gravitational pull, (c) pull-up from foreleg suspension, (d) effectiveness and latency of righting from a supine position, (e) effectiveness and latency of climbing a cage, (f) latency of stepping down from the platform suspended 6 cm above the ground when only the rat's hindlimbs were set on this platform, (g) visually elicited placing of the forelimbs when the rat is held down by the experimenter and slowly lowered toward the table surface, (h) proprio-
ceptive placing of the hindlimbs evoked by the pressure against the dorsum of the paw, when the rat is held up by the experimenter against the edge of a table, (i) proprioceptive stepping of the hindlimbs when the rat is being displaced by the experimenter from its center of gravity, and (j) attack elicited by touching the region of the rat's mouth or pinching the forelimbs with forceps.

Ten minute tests of the intake of highly palatable food and normal food pellets were given to each rat in the following order: Starting with the second postoperative day wet cookie mash was presented for 10 minutes, then the eaten amount was measured. On the following day the intake of the same cookie mash was evaluated, but after the intraventricular injection of NA, DA or both. On the next two days ordinary food pellets were presented, first without injections and then after intraventricular catecholamines. Such a sequence was repeated five times, i.e. up to the 21th postoperative day.

All these tests, as well as measurements of body weight and daily food and water intake, were conducted in each rat for 3 days prior to the lesion in order to establish a base line.

The experiment was performed on 5 groups of animals: (a) sham operated, receiving no intraventricular injections, (b) lesioned, receiving intraventricularly 0.5 μl of 0.9% NaCl, (c) lesioned, receiving intraventricularly 120 nmol of noradrenaline bitartrate in 0.5 μl of NaCl, (d) lesioned, receiving 120 nmol of dopamine hydrochloride in 0.5 μl of NaCl, and (e) lesioned, receiving 60 nmol of dopamine in 0.5 μl infusion and 10 min later the same amount of noradrenaline. In NaCl and NA receiving groups the tests were started 5–10 min after the injection, in DA group — 20 min after the injection, and in DA + NA group — 10 min after the second injection, in order to meet the maximal effects of the drug delivered.

Doses of drugs used in this experiment were established on the basis of preliminary tests. No difference was found between 60 and 120 nmol of intraventricularly given NA and both doses increased 10 min food intake to the same amount. After 180 nmol the amount eaten was half of the above due to the strong depression of muscular tone evoked by administration of NA. Shortly after the injection the rats became flabby and had great difficulty in the use of limbs. Sometimes they lay on the floor of the cage for several minutes and then they slowly approached the food container. This effect was dose-dependent: slight or absent after 60 nmol of NA, moderate after 120 nmol and strong in the case of 180 nmol.

Sixty nmol of DA had no influence on food intake, whereas 120

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nmol caused some effect. Muscular tone was not affected by DA in any dose.

Taking into account these preliminary results we decided to use 120 nmol of NA and DA in single injections and 60 nmol each of catecholamine in a combined injection as the optimal doses suitable for our purpose.

The results of the experiment were statistically analyzed with the use of the Mann–Withney U test (15).

![Graph](https://via.placeholder.com/150)

**Fig. 1.** Increase of intake of palatable food after intraventricular injections of catecholamines given to lateral hypothalamic rats (median + quadrilla deviation). Increase was evaluated in relation to intake without injection.

All the lesioned rats were aphagic and adipsic or hypophagic and hypodipsic postoperatively. Some required intragastric feeding and watering to keep alive. In all animals a loss of initial body weight was observed.

Although the damaged rats refused to eat ordinary food pellets, some of them being completely aphagic in the home cage for several days, they ate wet cookie mash in 10 min tests. The amount eaten could be heightened by intraventricular injections of catecholamines (Fig. 1). 120 nmol of NA increased the intake of palatable food by 29.5 ± 10.5%, and 120 nmol of DA — by 17.5 ± 6.5% as compared with eating without intraventricular injections. The most pronounced effect was observed after DA and NA given together, 60 nmol of each. The rats increased their intake of cookie mash by 47.0 ± 15.0% in comparison to non-injection eating, and this increase was statistically significant at the level of $P \leq 0.02$.

Intraventricular catecholamines also evoked the intake of normal
food pellets in 10 min tests: NA — mean 0.4 g, DA — mean 0.5 g and DA + NA — mean 0.6 g. Distinct differences between the groups are in this case difficult to evaluate, because the amounts eaten during ten minutes were very small, remaining within the limit of 1 g of pellets. However, observation of animal behavior indicated an increased alimentary activity in DA + NA group. These rats were more interested in pellets than the others, their latency of approaching the food container was shorter, and on return to the home cage when the 10 min test elapsed they were still looking for food. Even the completely aphagic rats searched for pellets after DA + NA injection, although they did not eat large amounts.

LH lesions produced various degrees of disturbances in animal sensorimotor abilities. Some rats seemed to be undisturbed, others were hyporeactive or unreactive to tactile stimulation whereas still others showed hyperresponsiveness and aversion to all stimuli. In none of the rats did we find deficiency in resistance to gravitational pull or in limb placing reactions.

In about half of the animals dramatic changes in the ability to initiate movement were observed. While lying supine or being suspended by the forelimb they did not try to right or pull themselves up for so long as 1 min (measurement of latency was ended when the rat did not move within 1 min). A similar impairment was seen after suspending the rat's hindlimbs 6 cm above the ground. In fact, the animals were able to correct their posture, because they did so effectively when activated. This cataleptic-like behavior did not closely parallel aphagia and adipsia.

Fig. 2. Latency of righting from a supine position in representative lateral hypothalamic rats receiving intraventricular injection of catecholamines. Dashed column, sham operated; white columns, lesioned without injection; striped columns, lesioned with injection.
Intraventricular injection of either catecholamine alone or of both together did not improve sensorimotor impairments in any test. Fig. 2 shows latency of righting from a supine position in the representative rat chosen in each group. As can be seen, NaCl, DA and DA + NA injections did not change this latency at all. NA delivered intracerebrally prolonged the latency, owing to its depressive influence on muscular tone. Neither was there any spontaneous recovery as long as 53 days after the lesion.

The results obtained showed that exogenous NA and DA can induce food intake in aphagic or hypophagic rats with the lateral hypothalamic lesions. This effect was more pronounced in the case of highly palatable food already accepted by damaged rats. Similarly as in intact animals (6), intracerebral NA increased eating to a greater degree than DA. Most interesting, however, was the finding of a positive interaction between NA and DA in respect of food intake during the lateral hypothalamic syndrome. Sixty nmoles of DA and NA injected together had a much greater effect on food intake than 120 nmol of each catecholamine given separately.

It should be stressed that in the preliminary test 60 nmol of DA did not influence food intake at all, although higher doses caused some effect. Therefore the result we observed after the combined NA + DA injections was not a simple summation of the effects, but rather a mutual potentiation of food intake-inducing action of each of the catecholamines.

The relative importance of NA and DA in food intake regulation remains an open question. In our as well as in other researches' experiments NA evoked greater eating than DA and smaller doses of the former are required to obtain a reliable response. On the other hand, Ungerstedt (17) proved that lateral hypothalamic aphagia can be attributed to the damage of the nigro-striatal dopaminergic pathway. It seems that efficient regulation of food intake depends on the integrality of both NA and DA pathways passing through LH. In fact, there is evidence that noradrenergic neurons derived from the locus coeruleus enhance impulse flow in the dopaminergic nigro-striatal system (5, 9, 13). Also pharmacological data indicate the stimulatory effect of NA on dopamine turnover in the brain and vice versa (2, 12). It is reasonable to assume that in our experiment noradrenaline and dopamine given together potentiated the action of each other and therefore had a greater effect on eating than when delivered separately. This may reflect a functional synergism between central NA and DA systems, which in normal conditions jointly determine the alimentary behavior.

As concerns other behavioral symptoms of LH lesions, not influenced by intracerebral catecholamines, they may be caused by destruction of
some other or more complex mechanism than simple disruption of
catecholaminergic pathways.

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