BRAIN NOREPINEPHRINE AND INGESTIVE BEHAVIOUR

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OVER the past decade, catecholamines have received considerable attention as possible mediators in brain-behavioural mechanisms. More specifically, there is evidence to suggest that brain norepinephrine (GROSSMAN, 1962) and dopamine (UNGERSTEDT, 1971) may have a functional role in the regulation of ingestive behaviour. Most studies concerned with this problem have administered drugs directly into the brain via chronically implanted cannulas and have observed their effects on behaviour. The studies to be described in this paper (LEIBOWITZ, 1972, 1973, and unpublished) examined, in the rat, the effects on feeding and drinking of centrally administered norepinephrine (NE), epinephrine (EPI), and dopamine (DA). Numerous areas of the brain were tested, in an attempt to determine a possible linkage between the catecholamine-induced behavioural changes and specific regions in the brain.

This work may be summarised as follows:

(1) Adrenergic stimulation of the 'perifornical' hypothalamus, at the level of the anterior hypothalamus, had profound effects on rat ingestive behaviour. Two of these effects, stimulation of feeding and suppression of drinking, were found to be mediated by alpha receptors. A third effect, the suppression of feeding, was found to be mediated by beta receptors.

(2) Examination of other ventral structures of the brain, extending from the pontine tegmentum to the caudate nucleus, revealed a consistent pattern of results with respect to ingestive behaviour. From the rostral midbrain to the preoptic area (and possibly the septum), the medial portion of the brain exhibited sensitivity only to alpha-receptor stimulation, whereas the lateral portion appeared to be sensitive only to the effect of beta-receptor stimulation.

(3) In my studies, dopaminergic stimulation of various diencephalic structures failed to have reliable effects on feeding or drinking.

For these investigations, albino rats were each stereotaxically implanted with a unilateral brain cannula under Nembutal anesthesia. After a week of post-operative recovery, the rats were tested while either food- and water-satiated, food-deprived, or water-deprived. With the use of a microsyringe, the drug or its vehicle, in a volume of 0·2 to 0·5 μl, was administered directly into the brain through the implanted cannula. After injection, the rats were given measured food and/or water, and their consumption was recorded at frequent intervals during the next 2hr.

Injection of NE or EPI into the 'perifornical' hypothalamus, immediately dorsal to the anterior hypothalamus, induced eating in fully satiated rats and potentiated feeding in already hungry rats. EPI, which proved somewhat more potent than NE, was effective in eliciting this response at a dose as low as 200 pmoles (66 ng). The magnitude of the response increased monotonically as the dose of EPI or NE increased to approximately 50 nmoles. This stimulation of feeding effect appears to

be mediated by alpha-adrenergic receptors, since it could be blocked by alpha-receptor antagonists but not by beta-receptor antagonists.

In addition to stimulating feeding behaviour, adrenergic stimulation of the perifornical hypothalamus had a strong suppressive effect on the water consumption of rats. This suppression of drinking phenomenon, which also increased monotonically with increase in dose, was reliably observed at a dose of EPI as low as 5 pmoles (1·7 ng). This dose, which is by far the lowest ever found to reliably alter behaviour, is much closer to probable physiological levels. This finding gives support to the hypothesis that adrenergic receptor mechanisms in the brain are physiologically active in the regulation of ingestive behaviour. Like the stimulation of feeding effect induced by NE or EPI, this suppression of drinking effect was found to be mediated by alpha receptors.

Under certain conditions, a third effect could also be induced by perifornical hypothalamic injections of EPI or NE. This effect was a suppression of feeding which these agonists were able to produce in hungry rats. This suppression was most readily seen at the higher doses of EPI or NE (20–100 nmoles) and was never reliably seen at doses below 5 nmoles (1·7 μg). Furthermore, in contrast to the alpha feeding stimulation effect, this suppression of feeding effect appears to be mediated by beta receptors, since it was blocked only by beta-receptor antagonists. The finding that alpha-receptor blockers could enhance the beta suppression effect, as well as lower its threshold dose, suggests that the relatively high doses required to observe the suppression may in part be due to the antagonism caused by the simultaneously occurring, and apparently more predominant, alpha stimulation of feeding effect.

Further work at a variety of central sites has indicated that different regions of the brain may be differentially sensitive to the effects of adrenergic stimulation. In experiments similar to those described above, NE and EPI, at a wide range of doses, were tested at seven different levels of the brain: (1) pontine tegmentum, (2) rostral midbrain tegmentum, (3) middle hypothalamus, (4) anterior hypothalamus, (5) preoptic area, (6) septum, (7) nucleus accumbens septi and caudate nucleus. At each level, two groups of rats were tested; one with a medial cannula (0·0–0·5 mm lateral, as determined histologically) and one with a lateral cannula (1·3–2·0 mm lateral, as determined histologically).

The results obtained in this study were remarkably consistent in differentiating the medial and lateral parts of the brain. It was found that at each of the levels extending from the rostral midbrain to the preoptic area, the two alpha-receptor phenomena, facilitation of feeding and suppression of drinking, could be elicited only with *medial* adrenergic stimulation; whereas the beta suppression of feeding phenomenon could be elicited only with *lateral* adrenergic stimulation. While the septum showed a tendency towards this pattern of sensitivity, the levels rostral to the septum and caudal to the rostral midbrain were found to be generally insensitive to adrenergic stimulation.

Although at several brain levels medial adrenergic stimulation was found to facilitate feeding in hungry rats, only at the level of the hypothalamus could such stimulation reliably initiate feeding in satiated rats. The most effective placement for eliciting feeding in satiated rats was found to be the paraventricular nucleus, which lies medial to the fornix at the level of the anterior hypothalamus. From these results on feeding behaviour, it becomes apparent that an on-going response can be

modulated by adrenergic stimulation at a wide range of medial sites, but that the initiation of a new response arises more specifically from adrenergic stimulation of the medial hypothalamus.

CONCLUSIONS

(1) It appears that the brain's sensitivity to alpha-adrenergic stimulation, which has reciprocal effects on ingestive behaviour (feeding facilitation and drinking suppression), follows a medial course from the rostral midbrain through the preoptic area (and possibly into the septum). The periventricular zone, which runs medially through each of these regions and which is very heavily innervated by adrenergic terminals, may possibly assume an important role in the mediation of these alpha-receptor effects on ingestive behaviour.

(2) In response to medial adrenergic stimulation, both the hypothalamic and the extrahypothalamic structures effectively *facilitated* the feeding of hungry rats. In satiated rats, however, only the hypothalamus was found to be reliably effective in *initiating* a feeding response. Within the hypothalamus, the paraventricular nucleus proved to be the most sensitive site for feeding initiation. This structure is part of the periventricular zone, an area generally sensitive for feeding facilitation. One can speculate that the paraventricular nucleus is a focal point for the initiation of a new feeding response.

(3) In addition to stimulating feeding behaviour, central adrenergic stimulation, under certain conditions, was found to suppress feeding behaviour. Areas of the brain sensitive to this suppressive effect, a possible beta-receptor phenomenon, are different from those sensitive to the alpha-receptor stimulation of feeding effect. The most effective regions were found to follow a lateral course from the rostral midbrain through the preoptic area and possibly into the septum.

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