NOREPINEPHRINE AND EPINEPHRINE IN THE CENTRAL NERVOUS SYSTEM

MARTHE VOGT

Department of Pharmacology, University of Edinburgh, Scotland

The object of this comment on Professor von Euler's paper is to discuss the question whether the norepinephrine found in the brain is entirely accounted for by the sympathin of the adrenergic vasomotor fibres or whether part of it may play a more direct role in the function of the central nervous system. As a first approach to this problem the distribution of norepinephrine was mapped out in the dog's brain. It was invariably found to occur together with small quantities of epinephrine, and the term "sympathin" will be used for this mixture. The methods are described in the detailed publication (1).

In the dog's brain, the highest concentration (1 μg norepinephrine/g fresh tissue) was present in the *hypothalamus*, about half that amount in the *grey stratum* around the *aqueduct*, a little less in the remaining midbrain, and still less (about 0.3 μg/g) in the floor of the fourth ventricle and in the *formatio reticularis* of the *medulla oblongata*. A non-nervous structure with a high content of sympathin was the *area postrema*. Except for the *medial nuclei* of the *thalamus* (content 0.23 μg/g), the remaining *diencephalon*, the entire *telencephalon*, the *cerebellum* and all myelinated fibre tracts examined contained no more than traces of sympathin (5–10 per cent of the hypothalamic concentration).

This distribution suggests that sympathin is not localized only in the vasomotor fibres. Its accumulation in all regions which contain, or are intimately connected with, the central representation of sympathetic activity suggests a possible role of sympathin in the function of the sympathetic centres.

Support for this interpretation was sought by examining the concentration of hypothalamic sympathin after the administration of drugs. The experiments were done on groups of cats subjected to the action of drugs for periods of 4–5 hours. Injected cats and controls were killed by bleeding in chloroform anesthesia. Of the 11 drugs tested, caffeine, leptazol, ephedrine, and ergometrine did not alter the concentration of hypothalamic sympathin, even if the doses used proved lethal. The remaining drugs all reduced the concentration of norepinephrine in the hypothalamus, the mean reduction in each group of cats ranging from 24 to 52 per cent. The drugs, in order of increasing potency, were apomorphine, ether, insulin, nicotine, morphine, β-tetrahydronaphthylamine and picrotoxin. Whenever the concentration of norepinephrine was reduced by a drug, the concentration of epinephrine was also lowered.

The question now arose what property was common to those drugs which caused a fall in hypothalamic sympathin and lacking in those which caused no such fall. There were convulsive drugs in both groups so that the production of convulsions was obviously not the decisive factor. Ether, insulin, nicotine, morphine, and β-tetrahydronaphthylamine, all members of the sympathin-depleting group, are known to cause secretion of hormones from the adrenal medulla by

central stimulation. Caffeine, leptazol, and ephedrine, which belong to the group that does not affect brain sympathin, have no such action. It was not known whether ergometrine or picrotoxin are capable of causing adreno-medullary secretion. An experiment was therefore carried out in which the action of ergometrine and of picrotoxin on medullary secretion was examined in rats. Picrotoxin, which lowers hypothalamic sympathin, also causes epinephrine secretion, whereas ergometrine has neither of these actions; the two actions appear to be correlated.

Further evidence pointing in the same direction was provided by experiments on cats which had been subjected to unilateral adrenal denervation. In such an animal, centrally evoked medullary secretion may be measured by determining the difference in amine content of the two adrenals which results from administration of a drug; any loss of hormone incurred by the innervated and not by the denervated adrenal medulla must have been caused by central action of the drug. In a series of 11 experiments, there were 5 cats in which the hypothalamic noradrenaline was not significantly depressed by the drugs employed (leptazol, caffeine, ether and ergometrine). In these animals, the amine content of the innervated adrenal amounted to more than 80 per cent of that of the denervated side. In the remaining 6 cats, in which apomorphine, β-tetrahydronaphthylamine and morphine were used, the concentration of hypothalamic noradrenaline fell to values ranging from 69 to 21.5 per cent of the normal. The corresponding figures for the amine content of the innervated adrenal (as percentage of the content of the denervated gland) lay between 68 and 14 per cent, the lowest figures occurring in those cats which also showed the greatest loss in hypothalamic sympathin; there is thus little doubt that, in the same animal, loss of hypothalamic sympathin is accompanied by a discharge of hormone from the innervated adrenal medulla.

The reverse is not necessarily true; occasionally adreno-medullary secretion was seen as a result of central drug action whilst the hypothalamic sympathin remained unaffected.

When the action of drugs on *mesencephalic* sympathin was examined, it was found to be influenced in the same way as was *hypothalamic* sympathin. In contrast, the sympathin in the *area postrema* remained unaltered after the administration of ether, morphine or apomorphine. It is suggested that the sympathin concentrated in the sympathetic centres has some role to play in the function of these centres, since part of it is lost when these very regions are stimulated by drugs.

REFERENCE

1. Vogt, M.: The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. J. Physiol., (In press).