THE DISTRIBUTION AND METABOLISM OF ADRENERGIC MEDIATORS

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We have listened to two comprehensive accounts of the physiology and pharmacology of the adrenergic chemical mediators, and it seems best for me to take up some of the points mentioned and try to enlarge upon them.

First—we should ask why adult guinea-pig and rabbit suprarenal glands contain epinephrine and only traces of norepinephrine in contrast to those of other species where the degree of methylation is much less complete. We thought we had part of the answer when the ratio of the size of the suprarenal cortex to that of the suprarenal medulla was calculated. This ratio is high (over 40) for the guinea-pig and rabbit, but near unity for the fowl and whale where the methylation is so incomplete. Intermediate ratio values fit well into this scheme (3). Besides, in patients dying of Addison's disease (where this ratio has been as low as 0.01), there is less methylation in their adrenals than is normally found (7). If our hypothesis had been proven, then the degree of methylation in the medulla would have been related to the relative size of the cortex, and the methylating enzyme, transmethylase, could conceivably have been a constituent of, or be activated by, cortical tissue. Further support was forthcoming when we examined the organs of Zuckerkandl of children aged less than 70 days and also the retroperitoneal tissue of many young mammals. Both of these abdominal accessory chromaffin tissues lack connection with the suprarenal cortical cells and were found to contain relatively large amounts of norepinephrine (4, 7). However, when tested in lower vertebrates where the inter-renal bodies representing the suprarenal cortex remain separated throughout life from the chromaffin bodies or rudimentary suprarenal medulla, epinephrine as well as norepinephrine was clearly identified and estimated. Two types of dogfish and the Torpedo were used for these experiments which were carried out simultaneously at Bari and at Dundee (6). The results leave no doubt that methylation of norepinephrine does not require the immediate presence of cortical tissue, although possibly a hormonal factor of cortical or pituitary origin may be necessary. A recent finding from our laboratory (1) that the organs of Zuckerkandl in children aged more than one year contain both epinephrine and norepinephrine supports this conclusion. The transient foetal adrenal cortex has by this time been replaced by the permanent adult cortex with its supply of cortical hormones.

Second—it is not surprising that norepinephrine has been linked with hypertension, since many features in hypertension seem to be consistent with an action of norepinephrine. However, we have now carried out analyses of urine from over 50 patients suffering from essential hypertension and only one has shown an abnormal excretion of norepinephrine (that is, over 100 μg per diem). This particular case later proved to be due to an adrenal medullary tumour, and in our hands the determination of urinary catechols is a screening test for pheochromocytoma which has not failed us so far.

Third—several workers have reported on the vasodilator action of norepinephrine. Is it not possible that this may be dependent upon the presence of small quantities of epinephrine in the blood? Occasionally, the vasodilator action is recorded early in experiments at a time when conditions are as near physiological as possible, and after 3 or 4 injections vasodilatation passes to vasoconstriction. Meier and Bein (2) in 1950 were the first workers to show that the normal vasodilator action of epinephrine in muscles depends upon the presence of norepinephrine in the blood stream, and it is possible that the presence of the former is necessary for the vasodilator action of the latter.

Lastly—everyone still talks about *l*-dopa decarboxylase but where is the DOPA? Although two reports have now appeared to show it to be present in mammalian tissues it has eluded us so far. We have been looking for it by paper chromatography, after subjecting animals to various procedures such as the administration of anti-metabolites (desoxypyridoxine, ethionine) or adrenal medullary stimulants (nicotine), but although the relative norepinephrine content of the adrenal gland has been altered no DOPA has been seen. Similar negative findings have been recorded in alloxan- or thiouracil-treated animals. We confirmed (5) that hydroxytyramine (or dopamine) is present in the adrenal medulla of the sheep, and wonder by reason of its absence in most other mammalian glands if it is not a by-product in the biosynthesis of epinephrine in the sheep. It is possible, of course, that we are completely wrong in our approach to the problem of formation of epinephrine. It may be, for example, simply a question of polypeptide chemistry.

REFERENCES

1. Hunter, R. B., MacGregor, A. R., Shepherd, D. M. and West, G. B.: Organs of Zuckerkandl and the suprarenal medulla. J. Physiol., 118: 11 P, 1952.
2. Meier, R. and Bein, H. J.: Der Einfluss der Nebennieren auf die Wirkung kreislaufaktiver Substansen. Helvet. physiol. et pharmacol. acta., 8: 436–453, 1950.
3. Shepherd, D. M. and West, G. B.: Noradrenaline and the suprarenal medulla. Brit. J. Pharmacol., 6: 665–674, 1951.
4. Shepherd, D. M. and West, G. B.: Noradrenaline and accessory chromaffin tissue. Nature, 170: 42, 1952.
5. Shepherd, D. M. and West, G. B.: Hydroxytyramine and the adrenal medulla. J. Physiol., 120: 15–19, 1953.
6. Shepherd, D. M., West, G. B. and Erspamer, V.: Chromaffin bodies of various species of dogfish. Nature, 172: 509, 1953.
7. West, G. B., Shepherd, D. M. and Hunter, R. B.: Adrenaline and noradrenaline concentrations in adrenal glands at different ages and in some diseases. Lancet, 2: 966–968, 1951.