REVIEW

The role of noradrenaline and other transmitter hormones in the pathogenesis of hypertension

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Summary

1. Studies with a sensitive radioenzymatic assay for plasma noradrenaline suggest there is a selective overactivity of the sympathetic nervous system in essential hypertension.
2. Serotonin turnover in the mesenteric vessels is approximately twice that of noradrenaline and it is suggested that serotonin may interact with noradrenaline to maintain vascular resistance.
3. Methodology which allows the study of local sympathetic turnover in nuclei of the central nervous system and in peripheral blood vessels is described. This approach has been used to study non-innervated sympathetic turnover observed in phaeochromocytoma.

Key words: hypertension, noradrenaline, phaeochromocytoma, serotonin, sympathetic drive.

Evidence is accumulating that increased sympathetic activity contributes to elevated blood pressure in essential hypertension (Louis, Doyle & Anavekar, 1973; Louis, Doyle & Jarrott, 1975). The precise mechanism is not yet clear and may not only involve the release of the transmitter noradrenaline but other hormones and transmitters such as the prostaglandins and serotonin. In addition non-autonomic factors such as structural changes and increased reactivity of blood vessels are also important in determining the final level of blood pressure.

Sympathetic overactivity

By the use of a sensitive radioenzymatic assay for plasma catecholamines it has been demonstrated that plasma noradrenaline concentration and dopamine-β-hydroxylase activity are elevated in patients with essential hypertension (Louis, Doyle, Anavekar, Johnston, Geffen & Rush, 1974). These results suggest that essential hypertension is associated with sympathetic overactivity. Moreover, this increased sympathetic drive must be selective as it is not associated with increased heart rate, cardiac output, plasma renin and other sympathetic functions and presumably selectively involves resistance blood vessels.

It seems, however, that the excess sympathetic drive is not by itself able to sustain the level of blood pressure seen in many patients with essential hypertension. Studies in normotensive subjects, and in patients with essential hypertension and in patients with depression (Louis, Doyle & Anavekar, 1975), indicated that eighteen of forty-four patients with essential hypertension had plasma noradrenaline levels in the normal range and an elevated mean blood pressure. In view of the complex release and inactivation mechanisms present at the nerve ending for noradrenaline, it could be argued that spill-over of noradrenaline into the plasma only occurs in the presence of a considerable increase in transmitter release. In addition the excess sympathetic drive may be acting in the presence of some other factor, perhaps causing a hyper-reactivity of blood vessels to pressor amines which augments its effect. This would be consistent with the idea that the level of blood pressure in man reflects both autonomic and non-autonomic components (Korner, Shaw, Uther, West, McRitchie & Richards, 1973).

Two questions remain: what additional peripheral factors may contribute to the maintenance of the hypertension and what is the nature of the increased sympathetic drive?
One additional peripheral factor which may be important is serotonin. There is considerable evidence that serotonergic neurons in the central nervous system are involved in the maintenance of vascular tone (Tabei, Spector, Louis & Sjoerdsma, 1969; Wing & Chalmers, 1974; Jarrott, McQueen, Graf & Louis, 1975a).

However, serotonin may also have a peripheral role in regulating vascular tone as was originally suggested by Page & McCubbin (1954). Serotonin receptors have been demonstrated in some blood vessels (Page, 1954) and other studies report that in genetic hypertensive rats and rats with deoxycorticosterone acetate-salt hypertension, some blood vessels (for example, mesenteric vessels) are supersensitive to serotonin (McGregor & Smirk, 1970; Haeusler & Finch, 1972).

Studies in the rat indicated that the turnover of serotonin in the aorta was 247 ng h⁻¹ g⁻¹ and in the mesenteric artery 303 ng h⁻¹ g⁻¹, which is approximately twice the reported turnover for noradrenaline. In other unpublished studies we have demonstrated serotonin in the blood vessels of the chicken, rabbit and man. Moreover, administration of the serotonin synthesis inhibitor p-chlorophenylalanine or the α-methylserotonin precursor α-methyl-5-hydroxytryptophan lowers blood pressure in experimental hypertension (Tabei et al., 1969; Jarrott et al., 1975a).

It is not clear in the rat whether the serotonin is present in the blood vessel wall or only in surrounding mast cells. However, serotonin was still detected in blood vessels after careful microdissection of the adventitia, suggesting that some serotonin is in the vessel wall. In either case it is possible to propose a vascular action for peripheral serotonin. In the rat, the mast cells are in such close proximity to the arteriolar wall and its adrenergic innervation (Furness, 1973) that they could easily influence vasoconstrictor tone, and even be under indirect autonomic control. For example, it has been demonstrated that endogenous substances such as ATP (Diamant & Kruger, 1967), prostaglandins and noradrenaline, which are known to be released during sympathetic activity (Hedqvist, 1973), will release serotonin from mast cells (Ladd & Chahl, 1974) and these substances could be a stimulus for the release of serotonin.

These results therefore raise the possibility that peripheral vasoconstriction by serotonin may be an important component of blood pressure maintenance.

Sympathetic drive

The nature of the increased sympathetic drive has not yet been resolved. Either an increased central sympathetic drive or a local disturbance in nerve endings in which a normal firing rate causes abnormal amounts of transmitter could explain the suggested increase in sympathetic drive. There is considerable evidence that normal vascular tone is regulated by a vasomotor centre in the brain stem and this area has noradrenergic and serotonergic pressor and depressor inputs (Wing & Chalmers, 1974).

Attempts have been made to develop methodology which allows the study of local sympathetic turnover in central nervous system nuclei and peripheral blood vessels (Axelrod, 1975; Jarrott, Tomlinson & Louis, 1975b). This approach has been used to study the non-innervated sympathetic tumour phaeochromocytoma (Jarrott et al., 1975b), and it is suggested that similar studies of local regulating mechanisms of neurotransmitter release would be valuable in other forms of hypertension.

Phaeochromocytoma

Tyrosine hydroxylase, dopa decarboxylase and dopamine-β-hydroxylase activities were measured in six phaeochromocytomas and in human adrenal glands and found to be three to ten times higher in phaeochromocytomas than in adrenal glands. On the other hand, the activity of monoamine oxidase in phaeochromocytomas was only 25% of normal activity. Since the enzyme monoamine oxidase is localized intracellularly in mitochondria, succinate dehydrogenase activity (a mitochondrial marker) was also measured and found to be reduced. This suggests a reduced number of, or severe damage to, mitochondria in the tumour cells. Mitochondrial damage was confirmed on electron microscopy (Watanabe, Burnstock, Jarrott & Louis, 1976).

The elevated activities of tyrosine hydroxylase, dopa decarboxylase and dopamine-β-hydroxylase in the tumours could explain the increased rates of synthesis and levels of catecholamines compared with adrenal glands. The reduced monoamine oxidase activity of tumours is of interest since this enzyme is believed responsible for breaking down
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FIG. 1. Topochemistry of catecholamine synthesis, storage and release in a normal adrenal medullary cell and a phaeochromocytoma cell. After the synthesis and storage of noradrenaline (NA) in the medullary cell, excess of NA in the cytoplasm is catabolized by mitochondrial monoamine oxidase (MAO) and possibly cytoplasmic catechol-O-methyl transferase (COMT) to an inactive metabolite that diffuses out of the cell. Release of NA together with ATP and dopamine-β-hydroxylase (DBH) is by nerve-mediated exocytosis from the storage vesicles. After synthesis and storage of NA in the non-innervated phaeochromocytoma cell, excess of NA in the cytoplasm formed by excess synthesis is not as extensively catabolized by MAO, owing to reduced activity of this enzyme, and therefore free NA, but not DBH, diffuses out of the cell thence into the circulation. ACH = acetylcholine.

excess ‘free’ noradrenaline in the cytoplasm, and its deficiency would enable newly synthesized noradrenaline to by-pass the saturated vesicle stores and diffuse out of the tumour cell into the circulation.

These data therefore support the suggestion that the hypertension in phaeochromocytoma results from excessive (adrenal) synthesis of catecholamines that by-pass the normal storage and secretion mechanism and diffuse into the circulation (Fig. 1). The results may explain some of the clinical features of the disease phaeochromocytoma, as well as the provocative actions of vasodilator agents such as histamine and glucagon in doses that do not release catecholamines from the adrenal medulla (Geffen, Rush, Louis & Doyle, 1973).

More importantly, the studies in phaeochromocytoma indicate the importance of local regulatory mechanisms in neurotransmitter release and show the need for similar studies in other forms of hypertension. Thus, in some circumstances, similar local defects in adrenergic neurons might give rise to elevated blood pressures independently of an increased sympathetic drive, whereas if they occurred in adrenergic neuron and nerve terminals in the central nervous system they might explain the increased central drive which it is suggested occurs in essential hypertension.

Acknowledgments

This work was supported by grants-in-aid from the National Heart Foundation of Australia and The Life Insurance Medical Research Fund of Australia and New Zealand. We are indebted to Professor R. C. Bennett, Department of Surgery, St Vincent’s Hospital, for supplying us with the human adrenal tissue.

References


