CENTRAL CATECHOLAMINES AND HYPERTENSION

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THERE appear to be two main themes in the session to ensue: (1) the central adrenergic actions of antihypertensive drugs such as α-methyl-dopa and clonidine; and (2) involvement of central and peripheral catecholamine mechanisms in blood pressure control and the pathophysiology of hypertension. I wish to begin the introduction of these subjects with a philosophic overview based on a personal long range interest in the ultimate target of our remarks, namely, the human patient with essential hypertension. I recall that early-on, at a time when no effective therapy was available and hypertension was a clinically-obvious killer, that visitors to our laboratory would frequently suggest that we should concentrate on finding the cause of hypertension, after which the cure would certainly follow. I had a number of angry responses to this naive suggestion, to whit, that people were dying because their blood pressure was too high and there was not time to wonder why, and besides we did not need to know the cause(s) in order to develop effective therapy, further that if we succeeded in controlling the blood pressure we would know more about etiology as a consequence, and finally that species variation in blood pressure responses were such that we intended to ignore animal pharmacology and follow directly into man leads provided us by catecholamine biochemists. This latter approach paid off in 1959 with our discovery in hypertensive patients of blood pressure lowering and sedative effects following administration of α-methyl-dopa (OATES *et al.*, 1960). It is of interest that, several years later, the same pharmacologic effects of clonidine were also first observed in man (GRAUBNER and WOLF, 1966). By 1966 we became sufficiently satisfied with the clinical therapeutic status to become interested in studying catecholamine metabolism in the spontaneously hypertensive rat (SHR) of Okamoto and Aoki and established a parent colony in the United States. Thereby, and with trepidation, we joined others on the primrose path of investigating the role of catecholamines in experimental hypertension.

In 1966 I expressed the opinion, based on extensive research findings in laboratory animals and man that "the effects of methyldopa are due to a combination of effects—including tranquilising and possibly as yet unknown actions in the central nervous system, peripheral transmitter depletion, possibly a substitute transmitter component, and perhaps even a slight inhibitory effect on catecholamine biosynthesis" (SJOERDSMA, 1967). It was of course clear by this time that α-methyl-dopa lowers blood pressure, not because it is a decarbozylase inhibitor, but because it is itself decarboxylated to α-methyl-dopamine which in turn is β-hydroxylated to the active product, α-methyl-norepinephrine. Subsequently, a mass of evidence has accumulated permitting the conclusion that acute hypotensive effects of methyldopa in animals are due to the formation of α-methyl-noradrenaline which acts at an α-adrenergic site in the brain, probably in lower brainstem. Findings leading to this conclusion were achieved by a variety of techniques including pretreatment with centrally-active decarboxylase

and β-hydroxylase inhibitors and α-receptor antagonists, and central routes of compound administration. Breakthrough evidence was provided by HENNING and RUBENSON (1971) and associates in Sweden, with independent parallel and confirmatory studies provided by HEISE and KRONEBERG (1972) in Germany, FINCH and HAEUSLER (1973) in Switzerland and others. Supportive evidence for central noradrenergic stimulation as a basis for blood pressure reduction comes from studies on clonidine, which will be discussed by Prof. Schwartz and others shortly.

I would now like to hark back to my earlier statement that improved treatment of hypertension with drugs might have etiologic implications. Certainly, the importance of surgical and later medical "sympathectomy" in therapy has been a potent stimulus to studies on catecholamine metabolism in the peripheral sympathetic system, both in human and experimental hypertension. Some of our speakers will address themselves to this problem and we can then judge the etiologic implications. But now that two of our best drugs, methyldopa and clonidine, have been shown to act on central catecholamine mechanisms, a huge effort focused on the role of catecholamines in the brain in blood pressure control and the etiology of hypertension is clearly warranted. What we hear to-day will only be the beginning. We began to focus on this latter area a few years ago and proposed in 1970 (YAMORI *et al.*, 1970) that catecholamines, while being pressor peripherally, may participate in a central depressor system. This hypothesis was based in part on suggestive evidence of decreased norepinephrine synthesis rates and concentrations in brainstem of the spontaneously hypertensive rat and was supported by the demonstration (YAMORI *et al.*, 1972) of a highly significant inverse correlation between levels of norepinephrine in brainstem, and blood pressure, in genetically hypertensive animals treated with various combinations of three drugs. These included a monoamine oxidase inhibitor, a peripheral decarboxylase inhibitor, and L-dopa.

Recalling the historical aspects again, I would like to conclude by re-emphasising the importance of studies in patients with hypertension. The burden is now on the clinical pharmacologist to ascertain whether the central actions demonstrated in laboratory animals account for blood pressure responses to clonidine and methyldopa in patients. It should be rather simple to ascertain whether the hypotensive effects of these drugs in man are antagonised by central receptor antagonists such as chlorpromazine, haloperidol and phenoxybenzamine. While I cannot recommend use of the vertebral artery or intracranial route of drug administration which has been so revealing in animal experiments, some of the same biochemical approaches used in patients with Parkinsonism could certainly be applied. In a similar vein, thought should be given to the possibility of a localised central catecholamine deficiency as an etiologic factor in patients with hypertension and an attempt made to study this in post-mortem material.

REFERENCES

FINCH L. and HAEUSLER G. (1973) *Br. J. Pharmac.* **47,** 217–228.
GRAUBNER W. and WOLF M. (1966) *Arzneim-Forsch. (Drug Res.)* **16,** 1055–1058.
HEISE A. and KRONEBERG G. (1972) *Europ. J. Pharmac.* **17,** 315–317.
HENNING M. and RUBENSON A. (1971) *J. Pharm. Pharmacol.* **23,** 407-411.
OATES J. A., GILLESPIE L., UDENFRIEND S. and SJOERDSMA A. (1960) *Science* **131,** 1890–1891.
SJOERDSMA A. (1967) In: *Supplement III to Circulat. Research*, **XX** and **XXI**, 119–125.
YAMORI Y., DE JONG W., YAMABE H., LOVENBERG W. and SJOERDSMA A. (1972) *J. Pharm. Pharmac.* **24,** 690–695.
YAMORI Y., LOVENBERG W. and SJOERDSMA A. (1970) *Science* **170,** 544–546.