A HYPOTHESIS FOR THE MODE OF ACTION OF α-METHYLDOPA IN RELIEVING HYPERTENSION

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There is evidence that α-methyldopa can serve as the precursor of α-methylnoradrenaline in the body. The α-methylnoradrenaline so formed may enter noradrenaline storage sites and then be released as a false neuro-transmitter. Because of the lesser potency of α-methylnoradrenaline there is some loss of responsiveness to sympathetic nerve stimulation which can explain the lowering of blood pressure in hypertensive patients.

THE relief of hypertension by treatment with α-methyldopa was first reported by Oates, Gillespie, Udenfriend and Sjoerdsma (1960). Subsequently, many more clinical observations have been made (amongst others; Irvine, O'Brien and North, 1962; Dollery and Harington, 1962; Smirk, 1963). Clinical reports describe α-methyldopa as a moderately active hypotensive drug with fewer side effects than guanethidine; the greatest advantage that α-methyldopa offers over guanethidine is that it produces a significant lowering of pressure in both standing and supine positions (Oates and others, 1960; Irvine and others, 1962).

Inhibition of Dopa Decarboxylase

One of the stages in the formation of noradrenaline, the transmitter at sympathetic nerve endings, is the decarboxylation of the amino-acid dihydroxyphenylalanine (dopa) to form the amine, dopamine (Fig. 1). Sourkes (1954) showed that α-methyldopa was a powerful inhibitor *in vitro* of the enzyme dopa decarboxylase. Oates and others (1960) confirmed that α-methyldopa inhibited decarboxylation of amino-acids in man. Treatment with α-methyldopa leads to the depletion of noradrenaline from its stores in the tissues and it is presumed that it is this depletion which leads to lowering of blood pressure in hypertensive patients. However, noradrenaline depletion does not seem to be a result of inhibition of dopa decarboxylase, since α-methyldopa did not reduce the excretion of metabolites of noradrenaline (Cannon, Whitlock, Morris, Angers and Laragh, 1962), which suggests that the production of noradrenaline *in vivo* is not impaired. Furthermore, Hess, Connamacher, Ozaki and Udenfriend (1961) reported that inhibition of dopa decarboxylase by α-methyldopa was a transient phenomenon whereas the depletion of noradrenaline was prolonged, and Gillespie, Oates, Crout and Sjoerdsma (1962) found that other substances which are known to be very potent inhibitors of dopa decarboxylase in man did not lower blood pressure.

Depletion of Noradrenaline Stores

α-Methyldopa not only depletes noradrenaline from stores in the tissues, but it also impairs the noradrenaline storage capacity of the tissues (Stone, Ross, Wengler, Ludden, Blessing, Totaro and Porter, 1962; Hess and others, 1961). However it has been reported that the depletion of noradrenaline by α-methyldopa is not accompanied by any obvious failure of responses to sympathetic nerve stimulation in experimental animals (Stone and others, 1962) and we have found that responses to tyramine are not greatly affected, and in these respects α-methyldopa

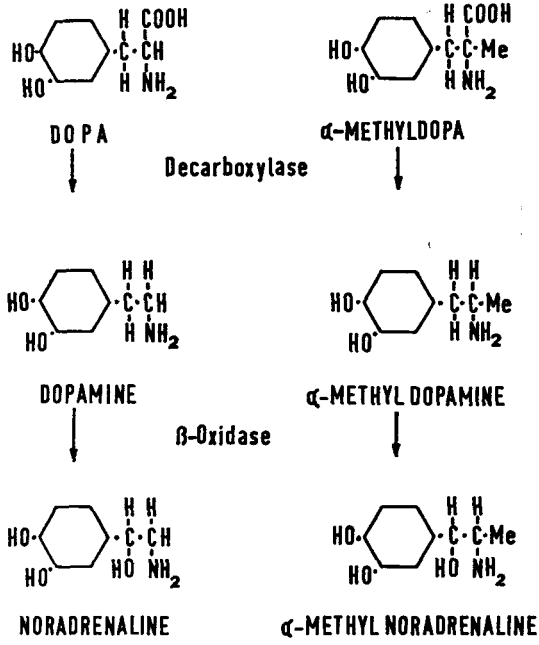

FIG. 1

differs from reserpine which causes depletion of noradrenaline and failure of responses to sympathetic nerve stimulation and to tyramine (Burn and Rand, 1958). Although Stone and others (1962) were unable to detect impairment of sympathetic nerve functioning after α-methyldopa in their experiments, the clinical findings indicate that in patients α-methyldopa causes at least partial sympathetic nerve blockade. Thus, postural hypotension and failure of ejaculation was reported by Gillespie and others (1962), and bradycardia and abolition of the overshoot in the Valsava manoeuvre was reported by Dollery and Harington (1962).

Responses to Sympathetic Nerve Stimulation after α-Methyldopa

We have confirmed the reports of others that α-methyldopa does not cause any striking effects indicative of sympathetic nerve blockage after

injection into conscious cats and rats; for example, it does not cause relaxation of the nictitating membrane. Nevertheless, in experiments in which we studied the contractions of the cat's nictitating membrane in response to stimulation of the postganglionic sympathetic nerves, we regularly observed an impairment of responses which was especially evident at low frequencies of nerve stimulation, although there was little or no impairment of responses to high frequencies of stimulation which produced maximal responses. Physiological rates of sympathetic nerve discharge are believed to be low. Therefore it seems likely that the impairment which we observed at low frequencies of stimulation can explain the clinical findings of sympathetic nerve impairment. The puzzling aspect of the pharmacological actions of α-methyldopa was that noradrenaline stores were depleted, yet responses to sympathetic nerve stimulation and to tyramine persisted.

Metabolism of α-Methyldopa

It has been shown that α-methyldopa can be decarboxylated to yield α-methyldopamine both in *in vitro* systems (Weisbach, Lovenberg and Udenfriend, 1960) and *in vivo* (Gillespie and others, 1962; Porter and Titus, 1963). There is evidence that the enzyme β-oxidase which converts dopamine to noradrenaline can convert α-methyldopamine to α-methylnoradrenaline (Fig. 1). Thus, Carlsson and Lindquist (1962) demonstrated the presence of α-methylnoradrenaline in the tissues of animals treated with α-methyldopa. Recently, Lauwers, Verstraete and Joossens (1963) found that in a patient treated with α-methyldopa there was what appeared to be an increased excretion of noradrenaline, but paper chromatography showed that there was another substance present, closely related but different to noradrenaline. Stott and others (1963) obtained high values for 3-methoxy metabolites resembling normetadrenaline in urine of patients on α-methyldopa and they showed that the high value was due to the presence of a substance having the properties of the 3-methoxy derivative of α-methylnoradrenaline.

We have obtained indirect evidence that α-methyldopa can be converted to α-methylnoradrenaline, and that the α-methylnoradrenaline formed can be utilised as a transmitter at sympathetic nerve endings. In animals treated with reserpine, noradrenaline stores are depleted and responses to sympathetic nerve stimulation or to indirectly acting sympathomimetic amines (such as tyramine) are greatly reduced or absent, then infusion of α-methyldopa causes a significant increase of these responses. Therefore α-methyldopa behaves like dopa, which also increases these responses in reserpine-treated animals (Burn and Rand, 1960), by increasing the noradrenaline stores (Pennefather and Rand, 1960). Partial restoration of responses to sympathetic nerve stimulation and to tyramine in reserpine-treated animals was also obtained after infusions of α-methyldopamine or of α-methylnoradrenaline. Our interpretation of these results is that after giving α-methylnoradrenaline, or its precursors, the noradrenaline storage sites are replenished with α-methylnoradrenaline, and that this substance then acts as the sympathetic transmitter.

Comparison of α-Methylnoradrenaline with Noradrenaline

That substitution of the false transmitter α-methylnoradrenaline for noradrenaline can lead to impairment of responses to nerve stimulation follows from its weaker activity. Ahlquist (1948) found that (±)-α-methylnoradrenaline had slightly less than half the potency of (±)-noradrenaline on the cat's nictitating membrane, and Goodman and Gilman (1955) state that corbasil ((±)-α-methylnoradrenaline) had slightly less than one quarter the potency of noradrenaline as a pressor amine. We have compared the pressor activity of (−)-α-methylnoradrenaline with (−)-noradrenaline and found it to have about half the potency in cats, about one-third in rats, and about one-sixth in guinea-pigs and rabbits.

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