Awakening from Reserpine Sedation by α-Methyldopa

SIR,—Rossum and Hurkmans (1963) found that α-methyldopa, given to mice pretreated with a monoamine oxidase inhibitor, produced central excitation. They suggested that this effect was due to the accumulation of catecholamines liberated from stores within the brain by the metabolic products of α-methyldopa. Their data are consistent with this suggestion. However, they stated that their experiments do not support the hypothesis of Day and Rand (1963) that α-methylnoradrenaline, formed by the metabolism of α-methyldopa, may serve in lieu of noradrenaline as a "false transmitter." The data of Rossum and Hurkmans are concerned only with actions of α-methyldopa exerted on the central nervous system, and are not necessarily applicable to actions of α-methyldopa at peripheral adrenergic junctions. The hypothesis advanced by Day and Rand (1963), was that a metabolic product of α-methyldopa (α-methylnoradrenaline) was able to occupy storage sites in peripheral tissues normally occupied by noradrenaline, and then to be available for release from these stores by stimuli normally leading to a release of noradrenaline. The important evidence for this hypothesis was derived in three ways: that α-methyldopa was able to enter the same metabolic pathways available for dopa, that one of the products, α-methylnoradrenaline was bound in tissues, and that infusion of α-methyldopa enhanced the responses to sympathetic nerve stimulation and to indirectly acting sympathomimetic amines in reserpine-treated animals. The first two points of evidence are derived from the biochemical work of others (cited in Day and Rand, 1963, and in Rossum and Hurkmans, 1963), the last is from our own experimental work. We have been unable to interpret it other than by assuming that α-methylnoradrenaline is able to serve as a transmitter at peripheral adrenergic junctions.

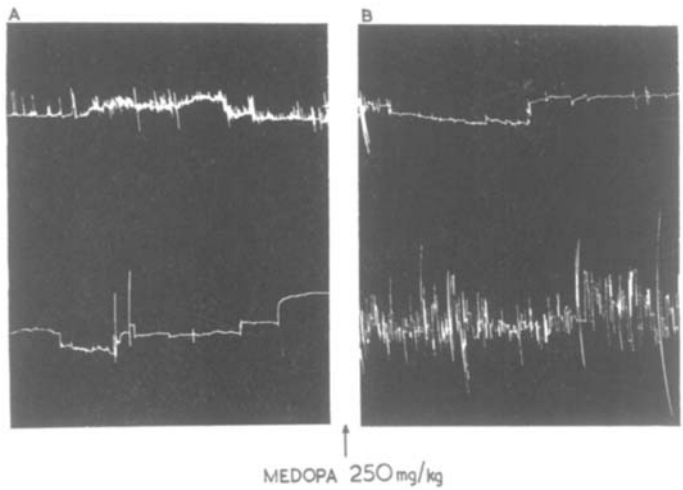

FIG. 1. Motor activity of two young litter-mate rats (55 g.) measured in jiggle cages (Brittain, 1961). Both rats pretreated 16 hrs. before the experiment with reserpine (15 mg./kg.) by intraperitoneal injection. In A both rats were heavily sedated and showed little spontaneous motor activity. Between A and B the rat in the lower record was injected with α-methyldopa (250 mg./kg.). After a period of 2 hr. the treated animal showed a marked increase in motor activity whilst the control (upper record) animal remained sedated.

In reserpine-treated mice, injections of dopa relieve the sedation and replete the stores of central catecholamines (Carlsson, Lindqvist and Magnusson, 1957; and Blaschko and Chruściel, 1960). In reserpine-treated rats which are heavily sedated, injections of α-methyldopa (250 mg./kg., intraperitoneally) caused a gradual increase in activity. The results from one experiment are illustrated in Fig. 1. Injections of α-methyldopa in rats not previously treated with reserpine decreased motor activity.

These observations may be interpreted in the following way. In normal animals, α-methyldopa is metabolised to yield α-methyldopamine and α-methylnoradrenaline. These amines replace the stores of dopamine and noradrenaline in the central nervous system (Carlsson and Lindqvist, 1962). The α-methylated amines may be able to serve in the same roles as dopamine and noradrenaline in the brain, but being less potent, sedation results. In reserpinised animals the stores of catecholamines in the brain are depleted and the animals are heavily sedated. Then, after α-methyldopa, the stores become replenished with the α-methylated amines and the sedation is relieved. It would follow from this explanation that the metabolic products of α-methyldopa may serve as "false transmitters" in the central nervous system as well as at peripheral adrenergic nerve endings. Carlsson and Lindqvist (1962) have also suggested that the α-methylated compounds which replace the catecholamines in the brain after treatment with α-methyldopa may take over the function of the physiological amines.

The excitement which Rossum and Hurkmans observed in mice pretreated with a monoamine oxidase inhibitor and then given α-methyldopa can best be explained by accumulation of catecholamines displaced from their stores but protected from destruction, but this explanation is not incompatible with the displacing α-methylated amines serving as a "false transmitter."

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