Antagonistic actions of α-methylnoradrenaline derived from α-methyldopa

In a recent paper van Miert & van Duin (1972) reported that α-methyldopa reduced or abolished the hyperpyretic response to bacterial or leukocytic pyrogen, and suggested that if this response is mediated by release of noradrenaline from adrenergic terminals in the hypothalamus the effect of α-methyldopa may be explained by intraneuronal formation of α-methylnoradrenaline and its subsequent release as a less potent false transmitter (Day & Rand, 1963). We would like to point out that α-methylnoradrenaline is not only a weak agonist of noradrenaline in the cns but is also an antagonist, and this property may be of significance in explaining the central actions of α-methyldopa.

The interactions of noradrenaline and α-methylnoradrenaline at the neuronal level were studied by Boakes, Candy & Wolstencroft (1968), using the iontophoretic technique in the brain stem of decerebrate cats. α-Methylnoradrenaline mimicked weakly the excitatory responses of neurons to noradrenaline but antagonized these responses when applied for longer periods; it was also a potent agonist of inhibitory responses of neurons to noradrenaline. These properties of α-methylnoradrenaline were also exhibited by metaraminol (Boakes, Bradley & others, 1971) and have been observed also in the brain stem of the anaesthetized rat (Walker, 1972). Although similar studies have not been carried out in the hypothalamus, iontophoretically applied noradrenaline has been shown to have both excitatory and inhibitory actions on hypothalamic neurons involved in thermoregulation (Beckman & Eisenman, 1970). Similar properties of α-methylnoradrenaline and metaraminol have also been observed in the spinal cord (Dhawan & Sharma, 1970) and in the areas concerned in thermoregulation (Dhawan & Dua, 1971). The latter authors found that α-methylnoradrenaline weakly mimicked the hyperthermic response of rabbits to intraventricularly injected noradrenaline but antagonized this response when injected with the noradrenaline.

In view of these findings we suggest that α-methylnoradrenaline, formed intraneuronally from α-methyldopa, could act as an antagonist of concomitantly released noradrenaline. Such an antagonism would be of significance in the abolition of the hyperpyretic effect of α-methyldopa reported by van Miert & van Duin. It is also possible that α-methylnoradrenaline plays a similar role in the hypotensive action of α-methyldopa. There is increasing evidence that replacement of noradrenaline in sympathetic neurons by the less potent false transmitter α-methylnoradrenaline does not account for the hypotensive action of α-methyldopa (Haefely, Hürlimann & Thoenen, 1967), but that a central mechanism involving α-methylnoradrenaline is involved (Henning, 1969; Finch & Haeusler 1972; Day, Roach & Whiting, 1972). The concept that α-methylnoradrenaline acts centrally as a partial agonist of noradrenaline (Stephenson, 1956), having antagonistic as well as weak agonistic properties, should be considered.

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Biphasic action of a 5-hydroxytryptamine inhibitor on fenfluramine-induced anorexia

Injections of the anorexic drug fenfluramine have a potent effect on brain 5-hydroxytryptamine (5-HT) metabolism (e.g. Morgan, Cattabeni & Costa, 1972), and also give rise to behavioural changes similar to those produced by 5-hydroxytryptophan (Southgate, Mayer & others, 1971). In experiments which have included measures of feeding activity, it has been reported that 5-HT inhibitors such as methysergide (Jespersen & Scheel-Krüger, 1970) or methergoline (Funderburk, Hazelwood, & others, 1971) antagonize the suppression of feeding behaviour induced by fenfluramine. In keeping with traditional pharmacological procedures for evaluating anorexic action, these experiments used only brief measures of food intake: appetite was restored by 5-HT inhibitors in dogs 1 h after fenfluramine injection and in rats during a 2 h feeding test. However, it has recently been shown that observation of the time course of food intake modulation represents a crucial aspect of the analysis of the central action of anorexic drugs (Blundell & Leshem, 1973). Accordingly the present experiment was designed to investigate the temporal relation of the action of a 5-HT inhibitor (methysergide bimaleate) on fenfluramine-induced anorexia.

Male black hooded rats, 350 g, kept in single cages, were given sham injections daily for 1 week before the start of the experiment. In the first experiment feeding was measured either following a period of 48 h food deprivation, or when the animals were satiated. Monitoring of feeding began 30 min after drug injections and measurements of food intake (to the nearest 0·1 g) were taken at 1, 4, 8, and 24 h. Animals received subcutaneous injections (0·1 ml volume) of either 5·0 mg kg^{-1} methysergide bimaleate or 0·9% saline in conjunction with intraperitoneal injections (0·5 ml volume) of either 5·0 mg kg^{-1} (±)-fenfluramine hydrochloride or saline.

In the second experiment, food deprived animals received injections of fenfluramine plus methysergide or fenfluramine plus saline. Food intake was measured for a 1 h period and the interval between injection and the beginning of the feeding test was fixed at 0·5, 1·5, or 2·5 h.

The results of the first experiment showed that although methysergide alone produced no apparent effect on food intake, this drug exerted a biphasic action on fenfluramine-induced anorexia (Fig. 1). In the first hour of the feeding test, methysergide clearly antagonized the appetite suppressant action of fenfluramine (Fig. 1a) and animals which received injections of methysergide plus fenfluramine consumed significantly more food than animals injected with saline and fenfluramine (Mann Whitney