NEUROTRANSMITTER MECHANISMS OF THE ACTION OF THE ANTIHISTAMINE DIMEBON ON THE BRAIN

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9-[2-(Methylpyridyl-5)ethyl]-3,6-dimethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride (dimebon) is a new Soviet antihistamine and antiallergic preparation [1]. In the character of its antihistamine action, it belongs to the H_1-histamine receptor blockers [4] and its antihistamine activity is 292 times stronger than that of diazoline (Omeril), 74 times stronger than diphenhydramine, 21 times stronger than phencarol (quinuclidyl-3-diphenylcarbinol), and 1.5 times stronger than promethazine [1, 5, 8].

Most modern antihistamines have characteristically a depressant action on the CNS [3, 6], which limits their potential use for out-patient treatment and makes these preparations less effective therapeutically.

The present writers have shown that dimebon, unlike diphenhydramine and promethazine, has no sedative action but, on the contrary, potentiates orienting-investigative activity of animals in the open field test. We know that the action of many antidepressants and CNS stimulants is connected with inhibition of monoamine oxidase (MAO) activity and accumulation of catecholamines and other biogenic amines in synaptic structures of the brain [2, 6, 7, 10, 11].

To discover the possible mechanism of the stimulating effect of dimebon on the CNS, the action of the drug was studied on catecholamine concentrations and turnover and activity of forms of MAO, differing in the substrate metabolized, in brain structures involved in the regulation of the emotional state (the cerebral cortex and hypothalamus) and in the regulation of motor activity (basal ganglia) [7, 10].

METHODS

The effect of dimebon on catecholamine metabolism and MAO activity in the brain was studied in 48 noninbred male rats weighing 210-230 g. Concentrations of noradrenalin (NA), dopamine (DA), and homovanillic acid (HVA) were determined fluorometrically [12]. Activity of MAO deaminating serotonin (MAO-S), dopamine (MAO-DA), and benzylamine (MAO-BA) was determined in homogenates of parts of the brain isolated by the method in [9]. ^{3}H-serotonin creatinine-sulfate (specific activity 17.8 Ci/mmole), ^{3}H-dopamine hydrochloride (7.4 Ci/mmole), and ^{14}C-benzylamine hydrochloride (50-60 mCi/mmole) (from Amersham Corporation, England), were used as substrates, under conditions of partial saturation of the enzyme by the substrates, whose final concentration in the incubation medium was 1/2 K_m of the corresponding substrate forms of MAO [7].

The numerical results were subjected to statistical analysis by Student's test.

RESULTS

In experiments *in vitro* dimebon, in a concentration of 10^{-4} M (Fig. 1), had an inhibitory effect on deamination of DA and benzylamine (BA) in homogenates of the cortex, hypothalamus, and basal ganglia, and only in the hypothalamus did it inhibit deamination of serotonin, but not significantly. In concentrations of 10^{-5} and 10^{-6} M the effect of dimebon on MAO

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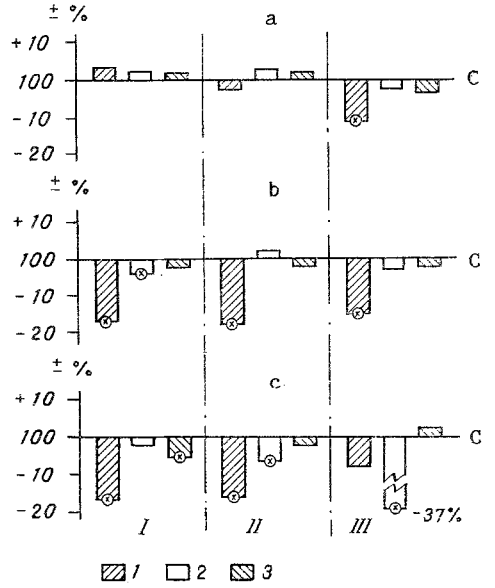

Fig. 1. Effect of dimebon *in vitro* on activity of substrate forms of MAO in homogenates of various structures of rat brain (in % of control): a) MAO-S; b) MAO-DA; c) MAO-BA. I) Cerebral cortes; II) basal ganglia; III) hypothalamus. C) Control (100%). Doses of dimebon 10^{-4} (1), 10^{-5} (2), and 10^{-6} M (3) respectively. *P < 0.01 compared with control.

activity was weakened or disappeared, and only in the hypothalamus was the greatest inhibition of MAO-BA observed in the presence of 10^{-5} M of the preparation. Dimebon had the strongest inhibitory action on deamination of BA and DA. Substrate forms of MAO in the hypothalamus were particularly sensitive to the inhibitory action of the preparation.

One hour after intraperitoneal injection of dimebon in a dose of 15 mg/kg, stimulating the orienting-investigative behavior of the animals, MAO-DA activity in the hypothalamus was reduced by 13%, MAO-DA and MAO-S activity in the basal ganglia was reduced by 22%, whereas MAO-DA and MAO-S activity in the cerebral cortex, on the other hand, was raised by 37 and 15% respectively (Fig. 2d).

The NA concentration in the hypothalamus of the rats 30 min after intraperitoneal injection of dimebon was increased, and after 60 min there was a considerable rise in the concentrations of NA (by 32%) and especially of DA (by 84%) in the cortex, whereas in the basal ganglia the level of HVA, the principal metabolite of DA, was lowered by 24%.

The most distinct inhibition of MAO (especially MAO-DA), accompanied by an increase in the concentration and weakening of the metabolism of DA and NA, was observed in the basal ganglia and hypothalamus. However, phasic changes in DA metabolism were observed in the cortex after injection of dimebon, evidence of an initial (after 30 min) enhancement of DA release (a tendency for the DA level to fall and the HVA level to rise), followed (after 1 h) by weakening of release of both DA and NA (a rise in the concentrations of both catecholamines). The increase in cortical MAO activity observed under these circumstances can be explained by the compensatory activation of the enzyme in response to initial enhancement of DA release.

Short-term activation of DA release of this kind in the cortical structures may evidently be one mechanism of the observed activating effect of dimebon on the CNS and on the orienting and investigative behavior of animals.

The results are evidence that dimebon, this new Soviet antihistamine, can inhibit MAO activity (especially MAO-DA and type B MAO) in the basal ganglia and other brain structures

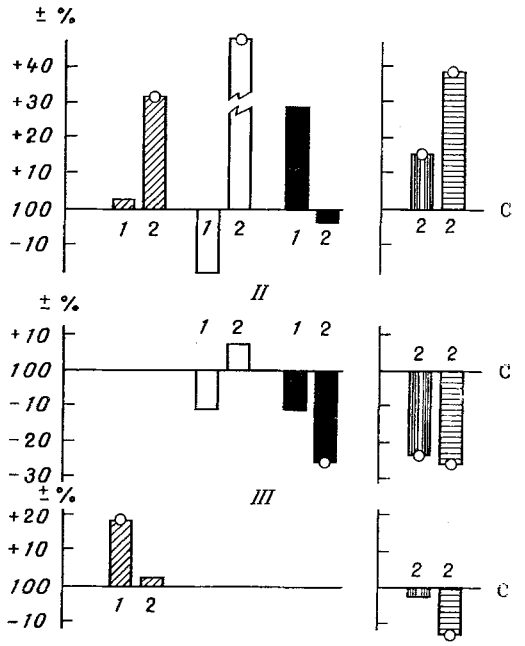

Fig. 2. Concentrations of NA (a), DA (b), and HVA (c), and MAO activity (d) in various structures of rat brain 30 min (1) and 60 min (2) after intraperitoneal injection of dimebon (± % of control). I) Cortex; II) basal ganglia; III) hypothalamus. Obliquely shaded columns, NA concentration (a); unshaded columns, DA concentration (b); black columns, HVA concentration (c); vertically shaded columns, MAO-S activity; horizontally shaded columns, MAO-DA activity. Remainder of legend as to Fig. 1.

both *in vitro* and *in vivo*, and can cause changes in DA and NA metabolism and in functional activity of catecholaminergic neuronal structures of the brain; these effects may lie at the basis of the activating effect of the drug on the CNS.

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