INHIBITION OF RAT BRAIN MONOAMINE OXIDASE BY REPEATED ADMINISTRATION OF PIRLINDOL

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Blocking monoamine oxidase (MAO) activity leads as a rule to changes in brain functions. MAO inhibitors, selectively blocking oxidation of biogenic monoamines, have been used in the treatment of depressive states and parkinsonism [2, 7].

The present writers have shown [3, 4] that the Soviet antidepressant pyrazidole (2,3,3a,4,5,6-hexahydro-8-methyl-1H-pyrazino[3,2,1-j,k]carbazole; international name pirlindol) inhibits deamination of several amines by MAO from rat brain, liver, and intestine in experiments in vitro and in vivo. Pirlindol is a selective, reversible type A MAO inhibitor [5]. This property of its action has been used in experiments in vitro and in vivo, with a single intraperitoneal injection of the drug into rats [5].

Since pirlindol, like other antidepressants, is used for a long time and since its therapeutic effect usually appears 5-7 days or more after the beginning of treatment [1, 2], it was interesting to investigate its action on activity of MAO of types A and B in rat brain when administered repeatedly.

EXPERIMENTAL METHOD

The effect of pirlindol on MAO activity of types A and B was studied in vivo on noninbred male rats weighing 180-200 g. Pirlindol, in a dose of 25 mg/kg, or isotonic NaCl solution (control) was given per os either once a day for 3 weeks, or repeatedly. The animals were killed 30 min and 3 and 24 h after the last dose of pirlindol.

MAO activity was determined in 50% homogenates of rat brain, made up in 10 mM phosphate buffer, pH 7.4, containing 2% detergent Triton X-100. The following amines were used as substrates in optimal concentractions for the given tissue (in micromoles per sample): serotonin creatinine-sulfate (from Reanal, Hungary) 12; dopamine-HCl (from Ferak, West Germany) 6; tyramine-HCl (from Merck, West Germany) 8; 2-phenylethylamine-HCl 0.8. MAO activity was determined by measuring ammonia liberated during incubation of the samples (final volume 1.8 ml) for 30 or 15 min, depending on the substrate used, at 37°C in an atmosphere of oxygen. Protein in 50% brain homogenates was determined by the method in [10]. Ammonia liberation in control samples during deamination of tyramine, serotonin, and dopamine amounted to 0.6, 0.36, and 0.36 μmole/mg protein/30 min respectively, and during deamination of 2-phenylethylamine it was 0.08 μmole/mg protein/15 min.

EXPERIMENTAL RESULTS

Data on inhibition of deamination of serotonin, tyramine, dopamine, and 2-phenylethylamine by MAO from rat brain homogenates by pirlindol after administration of single and repeated doses of the drug are given in Fig. 1. Maximal inhibition of deamination of serotonin and dopamine after a single dose of pirlindol was observed after 30 min (Fig. 1A). Dopamine, like serotonin, in the rat brain is mainly deaminated by type A MAO [6, 12].

After repeated administration maximal inhibition of deamination of serotonin, tyramine, and dopamine was observed 3 h after the last dose of pirlindol (Fig. 1b). If pirlindol was administered repeatedly, it retained its selectivity of action. For instance, 30 min after a single dose, when the maximal effect was observed, inhibition of deamination of serotonin and 2-phenylethylamine amounted to 33 and 14% respectively. Under chronic experimental conditions, 3 h after the last dose of pirlindol, it inhibited deamination of serotonin and

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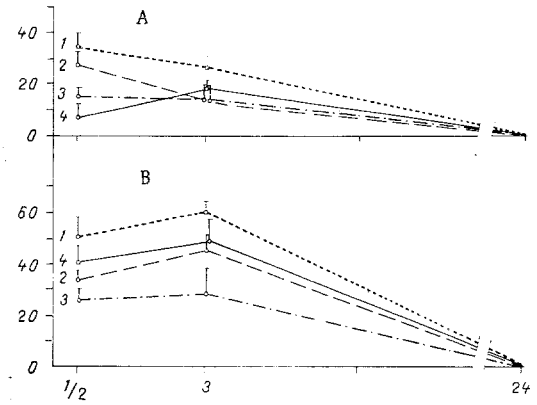

Fig. 1. Inhibition of deamination of various amines in rat brain by pirlindol when given as a single dose (A) and repeatedly (B). Abscissa, time after last dose of pirlindol (in h); ordinate, degree of inhibition of deamination (in %). 1) Serotonin, 2) dopamine, 3) 2-phenylethylamine, 4) tyramine.

2-phenylethylamine by brain homogenates by 59 and 28% respectively. The degree of inhibition of deamination of all the amines tested was 1.5-2 times greater in the case of repeated administration than administration of a single dose of pirlindol ($P < 0.05$). The inhibitory action of pirlindol on MAO activity ceased 24 h after the last dose of the drug.

The fact that pirlindol inhibits deamination of 2-phenylethylamine, although admittedly only to a relatively slight degree, can possibly be explained on the grounds that, in the concentration used to determine activity, 2-phenylethylamine is already partially deaminated not only by type B MAO, but also by type A MAO [11]. In our experiments we used 2-phenylethylamine in a concentration of $4.4 \cdot 10^{-4}$ M, which is oxidized by both types of MAO.

The results are evidence that pirlindol, when administered repeatedly to rats, preserves the selectivity of its action on type A MAO from rat brain demonstrated previously in the case of a single dose.

Acetylene inhibitors of MAO of types A and B, namely clorgyline and deprenyl respectively, when administered repeatedly (in doses of 1-10 mg/kg), usually lost their selectivity of action [8, 13]. Deprenyl preserved its selectivity of action against type B MAO only in a dose of 0.05 mg/kg when injected subcutaneously for 21 days [9]. The inhibitory effect of acetylene inhibitors usually lasts 2 weeks. So that their selectivity of action is preserved under these circumstances, careful choice of concentration is necessary [8].

Unlike acetylene inhibitors, the action of pirlindol is reversible. MAO activity is completely restored 24 h after the last dose of the drug under chronic experimental conditions. Pirlindol evidently exerts its influence on the serotoninergic and catecholaminergic systems of the body, for its administration causes an increase in the concentrations of serotonin, noradrenalin, and dopamine in certain parts of the animals' brain. A fall in the 5-hydroxyindoleacetic and dihydroxyphenylacetic acid levels was observed under these circumstances [2].

It can thus be postulated on the basis of these results that an important role in the antidepressant effect of pirlindol is played by its property of selectively blocking deamination of neurotransmitters such as serotonin and noradrenalin in the human brain.

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