EFFECT OF PSYCHOTROPIC DRUGS (CHLORPROMAZINE, MAJEPTIL, TRISEDIL) ON PROTEIN SYNTHESIS IN VARIOUS PARTS OF THE RAT BRAIN

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UDC 615.214.21.015.42:
612.82.015.348

Incorporation of methionine-S^{35} into total proteins isolated from various parts of the brain after a single injection of chlorpromazine, majeptil, and trisedil was investigated in experiments on rats. Generalized depression of protein synthesis in all structures except the medulla was observed 1 and 3 h after injection of chlorpromazine. In most experiments majeptil gave a stimulant effect. The action of trisedil was accompanied by reduced incorporation of methionine-S^{35} into proteins of most brain structures and increased incorporation in the olfactory lobes. It is postulated that changes in protein synthesis in individual brain structures are an important step in the mechanism of action of psychotropic drugs.

KEY WORDS: rat brain; protein synthesis; psychotropic drugs.

Most investigations, both in vitro [13, 15, 18] and in vivo [7, 9, 16, 17], point to inhibition of protein synthesis in brain tissue under the influence of chlorpromazine. However, some workers have described no change [2] or even stimulation of incorporation of labeled amino acids into brain proteins by chlorpromazine [12, 19]. The effect of other psychotropic drugs and, in particular, of majeptil and trisedil, widely used in clinical practice, on protein synthesis in the CNS has received very little study.

In the investigation described below the effect of three neuroleptics – chlorpromazine, majeptil, and trisedil – on incorporation of methionine-S^{35} into proteins of various parts of the rat brain was studied.

EXPERIMENTAL METHOD

Male rats weighing 180-250 g received a single intramuscular injection of chlorpromazine (10 mg/kg), majeptil (2.5 mg/kg), and trisedil (0.09 mg/kg), followed by intraperitoneal injection of a solution of methionine $-S^{35}$ with a total activity of 12 μCi. The animals were decapitated 3 h later, when the action of the drugs was at its height, and in the experiments with chlorpromazine some animals also were decapitated 1 h after the injection. Pieces of tissue from various parts of the brain were homogenized at 0-4° C with 10% TCA. Subsequent treatment of the tissue (precipitation of proteins with 5% TCA, extraction of lipids with ethanol and ether) was carried out in the usual manner. The radioactivity of dried preparations of the dry protein was measured on PP-8 and DP-100 radiometers with the aid of a T25-BFL end-type counter with a thin mica window (1.5 mg/cm^2). The specific activity was determined in counts per minute per gram protein, expressed as a ratio of the injected radioactivity per gram body weight, and the relative specific activity was calculated allowing for the radioactivity of the TCA-supernatant. The results of each series of experiments were subjected to statistical analysis by Student's method. Altogether 80 rats were used.

EXPERIMENTAL RESULTS AND DISCUSSION

After injection of chlorpromazine the sharp decrease in motor activity, muscle relaxation, and catalepsy was accompanied by a decrease in the incorporation of methionine-S^{35} into proteins in all brain

Group for Radiology Moscow Research Institute of Psychiatry, Ministry of Health of the RSFSR.
(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 79, No. 5, pp. 62-64, May, 1975. Original article submitted June 18, 1974.

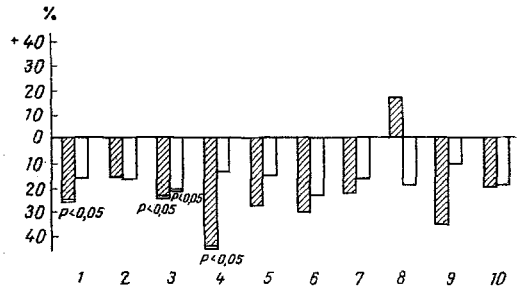

Fig. 1. Changes in incorporation (in %) of methionine-S^{35} into proteins of various parts of rat brain following administration of chlorpromazine: 1) cerebral cortex; 2) olfactory lobes; 3) hippocampus; 4) basal ganglia; 5) cerebellum; 6) corpora quadrigemina; 7) pons; 8) medulla; 9) spinal cord; 10) hypothalamus. Shaded columns after 1 h; unshaded columns after 3 h.

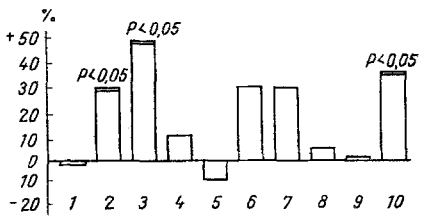

Fig. 2

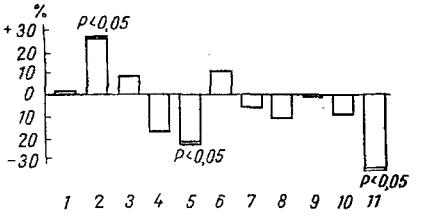

Fig. 3

Fig. 2. Changes in incorporation of methionine-S^{35} into proteins of various parts of rat brain 3 h after administration of majeptil. Legend as in Fig. 1.

Fig. 3. Changes in incorporation of methionine-S^{35} into proteins of various parts of rat brain 3 h after injection of trisedil: 5) thalamus; 6) cerebellum; 7) corpora quadrigemina; 8) pons; 9) medulla; 10) spinal cord; 11) hypothalamus. Remainder of legend as in Fig. 1.

structures studied (Fig. 1). A significant inhibition of protein synthesis was observed after 1 h in the basal ganglia, cerebral cortex, and hippocampus ($P < 0.05$). A tendency towards similar changes was found in all structures except the medulla. The decrease in methionine-S^{35} incorporation into brain proteins persisted 3 h after the injection of chlorpromazine. However, the changes were less marked and they were statistically significant ($P < 0.05$) only in the hippocampus.

The action of majeptil differed significantly from that of chlorpromazine. Against the background of marked catalepsy, the incorporation of methionine-S^{35} into proteins of most brain structures was increased at the time of maximal effect of majeptil (3 h). The greatest differences (by 35-50% compared with the control experiments) were observed in the hippocampus, hypothalamus, and olfactory lobes ($P < 0.05$). The figures for protein synthesis were not significantly different from normal in the cerebral cortex, spinal cord, and medulla, and only in the cerebellum was a small decrease in the incorporation of the label observed (Fig. 2).

In the experiments in which a compound belonging to the butyrophenone group (trisedil) was used, a significant decrease in protein synthesis in the hippocampus and thalamus and an increase in the olfactory lobes was observed 3 h after injection (Fig. 3). A tendency mainly for the incorporation of methionine-S^{35} into protein to fall was found in the remaining brain structures.

The results of these experiments show that each of the psychotropic drugs studied has a definite effect on protein synthesis, but not always the same effect in different parts of the brain. Chlorpromazine and trisedil had a mainly inhibitory effect, whereas majeptil had a stimulant effect. Opposite changes in protein synthesis were produced in brain structures by these two members of the phenothiazine series – chlorpromazine and majeptil – when given as a single injection. Examination of the mechanism of the

changes observed must take into account data on the inhibition of ATP formation and of oxidative phosphorylation in brain tissue by chlorpromazine [4, 5], which may give rise to a deficiency of the energy necessary for protein synthesis. Trisedil is also characterized by a reduced O_2 consumption in brain tissue [14], whereas majeptil may cause the development of tissue hypoxia [3]. Considering the data on a change in the RNA content in different parts of the brain [11] and inhibition of the incorporation of labeled precursors into RNA of the ribosomes [6, 8, 10, 11] by the action of chlorpromazine, the effect of the drug on protein synthesis in the brain may be considered to be exerted at the level of RNA synthesis.

The results suggest that changes in protein synthesis in individual brain structures under the influence of the three psychotropic drugs studied are an important step in the mechanism of their action on the body.

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