EFFECT OF SOME PSYCHOTROPIC DRUGS ON CENTRAL EFFECTS OF 5-HYDROXYTRYPTOPHAN IN RATS

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Antidepressants (imipramine, chloroacizine*), major tranquilizers (trifluoperazine, haloperidol, PVM), and minor tranquilizers (librium, meprobamate) prevent 5-hydroxytryptophan hyperkinesia but do not affect the hypothermia induced by 5-hydroxytryptophan. Antidepressants and minor tranquilizers prevent, but major tranquilizers do not change the depriming effect of 5-hydrotryptophan on conditioned defensive reflexes.

The influence of psychotropic drugs on the central effects of serotonin have been described [2, 4, 7]. However, the role of their interaction with the serotonin receptors of the brain in the development of the psychotropic effect has not yet been elucidated. In attempts to solve this problem, many workers have studied the antiserotonin action of only one group of psychotropic drugs, and usually for this purpose they have limited their attention to only one of the central effects of serotonin [10, 14, 15].

A more useful approach to the investigation of this problem appeared to be a study the effect of not one, but of several groups of psychotropic drugs on various central effects of serotonin.

EXPERIMENTAL METHOD

Experiments were carried out on sexually mature rats weighting 150-200 g. Of the central effects of serotonin, consideration was paid to the motor (hyperkinesia), autonomic (hypothermia), and behavioral (inhibition of the conditioned defensive reflex) responses. Serotonin receptors were stimulated by 5-hydroxytryptophan (5-HTP), which is converted into serotonin in the CNS [3]. Of the psychotropic drugs, the major tranquilizers (trifluoperazine, haloperidol, PVM†), the minor tranquilizers, librium, meprobamate), and antidepressants (imipramine, chloracizine) were used. The psychotropic drugs were injected intraperitoneally 20 min before 5-HTP. Hyperkinesia was induced by injection of 5-HTP (300 mg/kg). The effect was recorded 20 min after injection of 5-HTP for 5 min. The action of the psychotropic drugs on hypothermia induced by 5-HTP (150 mg/kg body weight) was estimated from the change in rectal temperature, measured every 30 min for 3 h after injection of the serotonin precursor. The conditioned defensive reflex was formed by the method of Cook and Weidley [5]. The effect of the drugs on the ability of 5-HTP (150 mg/kg) to block the conditioned defensive response was noted every 30 min for 4 h. The dose of the drugs chosen initially was that which blocked 5-HTP hyperkinesia in 50% of the animals (ED_{50} by the method of Litchfield and Wilcoxon [11]). When the effect of the compounds on changes in behavioral and autonomic responses to 5-HTP were investigated, the doses were those which, when given alone, had no effect on the indices studied.

Intraventricular injection of 5-HTP (4 mg in the crystalline form) was carried out through cannulas introduced into the lateral ventricle in accordance with the coordinates of De Groot's atlas [8].

*2-Chloro-10-(3-dimethylaminopropionyl)phenothiazine.

†A phenothiazine derivative and the analog of dixyrazine.

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TABLE 1. Effect of Some Psychotropic Drugs on Motor, Autonomic, and Behavioral Responses to 5-HTP in Rats

Name of drug	Doses of compounds blocking 5-HTP hyperkinesia in 50% of animals (in mg/kg, intraperitoneally)	Deviation of temperature from original value (in deg)				Conditioned defensive reflex (ratio between number of animals with inhibited reflex and total number of animals in test)			
		effect of 5-HTP	dose of comp. (mg/kg) intraperitoneally	effect of compound	effect of 5-HTP 1 h after injection of comp.	effect of 5-HTP, 150 mg/kg	dose of comp. (mg/kg) intraperitoneally	effect of compound	effect of 5-HTP 1 h after injection of comp.
Imipramine	19,5(10,0—38,0)	—1,2±0,3	1	+1,2±0,76	—0,7±0,18	8/9	5	0/9	3/9[1]
Chloracizine	72,0(61,5—84,2)	—1,2±0,5	20	—0,6±0,2	—1,4±0,5	6/6	20	0/9	6/15[1]
Librium		—1,1±0,2	15	—0,7±0,2	—1,3±0,1	14/15	15	0/6	0/11[1]
Meprobamate	87,0(43,5—174,0)	—1,3±0,3	45	—0,3±0,3	—1,9±0,4	14/15	45	0/6	2/12[1]
Trifluoperazine	0,54(0,31—0,94)	—1,4±0,4	0,27	+0,7±0,5	—0,6±0,3	6/6	0,27	0/6	8/9
Haloperidol	0,16(0,009—0,28)	—2,1±0,3	0,08	—0,5±0,5	—2,1±0,3	6/6	0,08	0/6	9/9
PVM	11,0(6,6—18,4)	—1,9±0,2	5,5	—0,4±0,2	—2,1±2,0	6/6	5,5	0/6	7/9

*Conditioned defensive reflex (ratio between number of animals with inhibited relfex and total number of animals in test).

In the experiments of series I the effect of the psychotropic drugs on 5-HTP hyperkinesia was studied. In a dose of 300 mg/kg, 5-HTP induced characteristic spasms of the head in all animals in the experiment. According to Corne et al. [6], 5-HTP hyperkinesia is due to the action of endogenous serotonin on the brain stem. The present experiments in which 5-HTP was applied to the floor of the lateral ventricle confirmed the central origin of this phenomenon. In this case, hyperkinesia developed in the first 2-3 min, whereas after intraperitoneal injection of 5-HTP it developed later (after 13 ± 1.6 min). All the compounds tested, except librium, revealed clear antiserotonin properties in the 5-HTP hyperkinesia test (Table 1). The combined administration of librium and 5-HTP was toxic for the rats, so that the antiserotonin properties of the compounds could not be detected by this test. The serotonin-negative activity of the psychotropic drugs as shown by the 5-HTP hyperkinesia test was evidently specific, for these substances had no effect on the reflex from the concha auriculae in doses completely suppressing hyperkinesia.

5-HTP is known to give rise to considerable changes in activity of the autonomic nervous system [9]. In particular, in experiments on small laboratory animals it has a clear hypothermic action. In the present experiments, 60 min after intraperitoneal injection of 5-HTP (150 mg/kg) the body temperature was lowered by 1.4 ± 0.6°C. The hyperthermic effect of 5-HTP persisted for 2 h. The cause of the 5-HTP hypothermia has not yet been finally settled. However, according to some investigations the hypothermic action of 5-HTP is most probably central in origin [1, 12, 13]. The present experiment showed that the lowering of body temperature produced by 5-HTP takes place not only after intraperitoneal, but also intraventricular injection. In the latter case, marked hypothermia, amounting to 3 ± 0.8°, developed during the first 10 min after injection of the compound, whereas if injected intraperitoneally, it developed by the end of the first hour.

The study of the effect of psychotropic drugs on hypothermia induced by 5-HTP showed that not all the compounds prevent this effect of 5-HTP (Table 1).

One of the central effects of 5-HTP is its depriming action on its conditioned defensive reflex [5]. In the present experiments, 5-HTP (150 mg/kg) inhibited a conditioned-reflex avoidance response in all the rats. The action of the compound continued for 1-1.5 h. Minor tranquilizers and antidepressants reduced or completely blocked the action of 5-HTP on the conditioned reflex. Unlike them, the major tranquilizers revealed no definite antiserotonin property in this test (Table 1).

Hence, the results of these experiments showed that the antiserotonin activity of the tested compounds is determined by the localization of the serotonin receptors in the CNS, and by the character of their psychotropic activity. In fact, all the tested drugs (antidepressants, major and minor tranquilizers) had no effect on serotonin-sensitive structures in the region of functional brain systems participating in the genesis of 5-HTP hypothermia. On the other hand, the psychotropic compounds of all three groups blocked the sensitivity of serotonin

receptors involved in the development of 5-HTP hyperkinesia. Serotonin receptors located in the region of brain systems participating in the inhibition of the conditioned defensive reflex exhibited unequal sensitivity to these drugs. The major tranquilizers had no effect on these structures, while the minor tranquilizers and antidepressants inhibited them. The compounds studied possess serotonin-negative properties within that dose range in which they usually exhibit their characteristic pharmacological action.

It is difficult at present to identify the role of their antiserotonin activity in the mechanism of action of tranquilizers and antidepressants. These experiments have shown that psychotropic compounds of different action may exert the same serotonin-negative effect in the region of the same functional brain systems. Consequently, there are no grounds for considering that the character of their action on the central nervous system can be determined entirely by this one property of these drugs. However, the possibility is not ruled out that the central antiserotonin properties may be important for the manifestation of some aspects of the psychotropic activity of these drugs.

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