RECIPROCAL RELATIONS BETWEEN MONOAMINERGIC BRAIN SYSTEMS AS A FACTOR IN PHARMACOLOGICAL COMPENSATION OF BEHAVIORAL DISTURBANCES INDUCED IN ANIMALS BY 6-HYDROXYDOPAMINE

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Previous investigations in the writers' laboratory showed that reciprocal interaction between the serotoninergic (5-HT) and noradrenergic (NA) brain systems are involved in the regulation of emotional behavior and learning in animals [1, 2]. As a result of this reciprocity, the same effect on animal behavior can be obtained either by increasing the activity of one of these systems or reducing the activity of the other. These observations are of great importance for pathology in connection with dysfunction of monoaminergic (MA) brain systems and for the correct choice of pharmacological approach to the treatment of different forms of diseases.

This paper gives experimental data reflecting the important role of reciprocal relations between the above-mentioned systems in compensation of disturbances of animal behavior by the use of substances intervening in catecholamine and serotonin metabolism.

EXPERIMENTAL METHOD

Experiments were carried out on 54 male Wistar rats: control animals and rate with chronic deprivation of activity of catecholaminergic (CA) systems caused by neonatal administration of 6-hydroxydopamine by the method described previously [4]. The experimental model used in the investigation was the frustration reaction arising in animals in experiments to produce goal-directed visits to a place where food could be obtained, and with a sudden reduction in magnitude of the food reinforcement. Experiments were carried out on animals aged 4 months in a special chamber measuring 150 × 16 × 23 cm, divided into three compartments: start, central, and goal. On the boundaries between these compartments photoelectric cells were fixed in the walls of the chamber to record the animal's reaction time in each compartment. The level of motivation before the experiments began corresponded to a 15% loss of body weight of the animals. The reaction was formed in the course of 5 days and every day the animals made five visits, obtaining food reinforcement in the goal compartment in the form of 500-mg bread pellets. The magnitude of food reinforcement was then suddenly reduced by 10 times (to 50 mg) and the rats continued to make five visits, with this low level of reinforcement, for 5 days. They developed a frustration reaction under these conditions, which was assessed as the change in the time of going from the start compartment into the goal compartment to obtain the food reinforcement. The frustration reaction was expressed quantitatively as a coefficient K_f, calculated by the equation:

$$K_f = \frac{T_2 - T_1}{T_1},$$

where T_1 is the time taken to perform the reaction before reduction of the reinforcement, T_2 the time of its performance after reduction of the reinforcement.

Intervention in activity of the MA systems was carried out by the use of drugs affecting monoamine biosynthesis: L-dopa (5 and 20 mg/kg, intraperitoneally, daily, 1 h before the experiments), dihydroxyphenylserine (DOPS, from "Serva," West Germany, 50 mg/kg intraperitoneally, daily 1 h before the experiments), parachlorophenylalanine (PCPA, from "Koch-Light," England, 320 mg/kg intraperitoneally, 3 days before the experiments and thereafter at intervals

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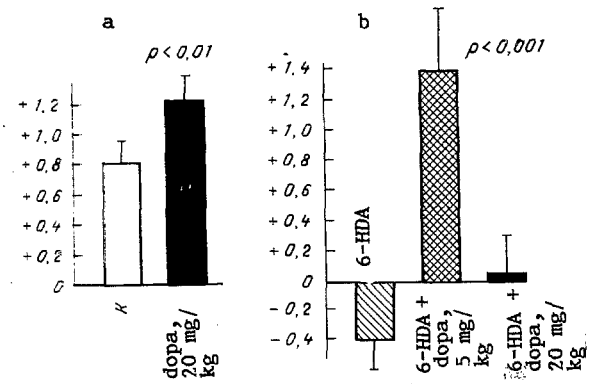

Fig. 1

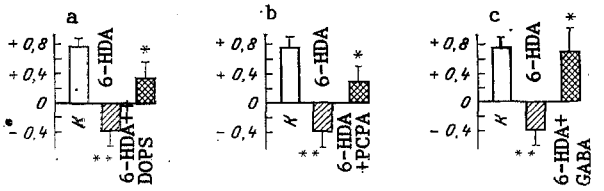

Fig. 2

Fig. 1. Changes in frustration in reaction in intact rats (a) and rats with chronic deprivation of activity of the brain CA systems (b) by injection of dopa in doses of 20 and 5 mg/kg. Here and in Fig. 2: K) control. Ordinate, coefficient of frustration.

Fig. 2. Recovery of frustration reaction in rats with chronic deprivation of activity of brain CA systems by injecting animals with: a) DOPS, 50 mg/kg; b) PCPA, 320 mg/kg; c) GABA, 50 mg/kg. *p<0.01 compared with intact control, **p<0.01 compared with group of deprived rats.

of 5 days), gamma-aminobutyric acid (GABA, aminalon, USSR, 50 mg/kg intraperitoneally, daily 30 min before the experiments), and 6-hydroxydopamine (6-HDA, from "Sigma," USA, 100 mg subcutaneously, daily during the first 3 days after birth).

Biochemical investigations of monoamine concentrations in the neocortex of the control and experimental animals were undertaken by a fluorometric method after the end of the behavioral experiments [3].

The results were subjected to statistical analysis on "Élektronika-60" minicomputer, using Student's t test.

EXPERIMENTAL RESULTS

Biochemical analysis of concentrations of biogenic amines in the neocortex of animals receiving 6-HDA after birth showed that neonatal administration of this compound is accompanied by a long and selective decline of the catecholamine level without any change in the 5-HT concentration. In animals aged 4 months, the catecholamine concentration in the neocortex was reduced by 100%, whereas the 5-HT concentration was the same as in the control animals.

A study of behavior of the animals showed considerable differences. In the control animals a sudden reduction of food reinforcement caused marked slowing of the visit to the goal compartment, evidently due to the appearance of frustration, and reflected in an increase in K_f (Fig. 1a). By contrast with this, animals with chronic deprivation of activity of the CA systems hardly reacted at all to reduction of the food reinforcement, and in some cases they exhibited a paradoxical reaction, expressed as quicker performance of the food-getting reaction. Correspondingly, K_f became negative in value (Fig. 1b).

To normalize the disturbances of the balance between activity of the 5-HT and CA systems of the brain, experiments were carried out with substances lowering the brain catecholamine level, namely L-dopa and DOPS. Injection of L-dopa (20 mg/kg) into the control and experimental animals was accompanied by different effects. In the control animals this dose of L-dopa caused considerable intensification of the frustration reaction, reflected in an increase in K_f (Fig. 1a). Injection of the same dose of L-dopa into the deprived animals caused a very small increase in K_f, and the animals' behavior was characterized by marked hyperactivity and by its chaotic nature (Fig. 1b). Taking account of data showing an increased sensitivity of receptors of the pre- and postsynaptic membrane of NA synapses in the cortex of animals receiving 6-HDA [10], the dose of L-dopa was reduced in the next experiments. Injection of L-dopa in a dose of 5 mg/kg into rats with chronic deprivation of the CA systems was followed by recovery of the frustration reaction, and K_f became positive again (Fig. 1b).

In experiments in which the deprived animals were given DOPS, which induces selective evaluation of the brain noradrenalin level [5], the effect obtained was similar to that of the small dose of L-dopa (Fig. 2a). This similarity between the effects of L-dopa and DOPS in-

dicates that recovery of the frustration reaction in the deprived animals was mainly linked with elevation of the noradrenalin level.

Because of the postulated reciprocal character of functional relations between 5-HT and NA systems of the brain [2], experiments of series III were undertaken, with selective depression of activity of the 5-HT system by injection of para-chlorophenylalanine, an inhibitor of 5-HT biosynthesis. The results of these experiments showed that injection of PCPA into the deprived animals was followed by normalization of their behavior; the frustration reaction was restored and the value of K_f became positive (Fig. 2b).

Because of the above results, it was interesting also to study the effect of GABA, which has opposite effects on activity of the 5-HT and NA systems of the brain, lowering the brain 5-HT level [9] but raising the NA level [6], on the behavior of the deprived animals. The results of the corresponding experiments showed that injection of GABA into animals with deprived activity of the CA systems is accompanied by restoration of the frustration reaction, characterized by a high value of K_f (Fig. 2c). It can be concluded that compensation of disturbances of animal behavior due to deprivation of activity of the CA systems can be achieved both by increasing activity of the NA system by means of L-dopa and DOPS, and by reducing activity of the 5-HT system with the aid of PCPA. This similarity between the positive effects of these substances can be explained by the existence of reciprocal relations between the NA and 5-HT systems of the brain [1, 2], which have anatomical [7] and biochemical [8] connections ensuring mutual regulation of activity of the nuclei raphe and the locus coeruleus.

The results demonstrate the importance of reciprocity of the serotoninergic and noradrenergic systems of the brain in compensation of disturbed animal behavior and they indicate the importance of taking this reciprocity into account during pharmacological correction in diseases associated with an imbalance between the NA systems.

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