ROLE OF THE BRAIN DOPAMINERGIC SYSTEM IN GENERALIZATION

E. I. Mukhin and O. S. Adrianov*

UDC 612.821.2.014.46:615.217.32

KEY WORDS: generalization; dopaminergic and cholinergic system; frontal cortex; caudate nucleus; compensation.

The aim of this investigation was to study the effect of certain dopaminergic and cholinergic substances on generalization and abstraction processes in intact cats and after destructive operations on the brain. The grounds for the investigation were the hypothesis that the monoaminergic neurotransmitter system is connected with psychopathology in man [4, 7].

EXPERIMENTAL METHOD

Experiments were carried out on 13 unrestrained cats [5]. The animals were first taught to choose (from a starting cage) the side of food reinforcement, which was hidden behind a screen (length 1.5 m, height 1 m), when one of two initial geometric figures (circles), differing only in size, was presented at its edge; the larger circle on the right and the smaller on the left side. Later, new figures were presented specially in the midline of the screen, but with an initial alternative. In other words, the animal had to pick out the essential features of the stimuli (size, for example) and to generalize them, "abstracting" from other secondary characteristics (color, shape, etc.; under normal conditions, such problems are solved at a level statistically significantly higher than random decisions). In the course of a subsequent surgical operation, bilateral injury was inflicted on the head of the caudate nucleus and proreal gyrus in different orders. The role of the cholinergic and dopaminergic systems of the brain in the responses described above was analyzed by the following scheme: bilateral injection (through a microcannula) into the caudate nucleus of 7 µl of 0.05% neostigmine (acetylcholinesterase inhibitor) solution, 7 µl of 0.1% atropine (cholinolytic), and 100-150 µg dopamine. Haloperidol (neuroleptic) was injected intraperitoneally into the intact animals and those with brain damage in a dose of 0.3 mg/kg together with atropine 0.3 mg/kg and scopolamine 0.3-0.5 mg/kg.

EXPERIMENTAL RESULTS

Pharmacological stimulation of the cholinergic system of the caudate nucleus with neostigmine caused disturbances of problem solving in generalization (Fig. 1A, c) followed by recovery of goal-directed behavioral acts after 30-60 min (Fig. 1B, c).

Microinjection of atropine, which blocks cholinergic reception, into the head of the caudate nucleus had no such effect. Problem solving in generalization was successful at the level of 60% or higher (Fig. 1A, B, a). Activation of dopaminergic structures of the caudate nucleus by microinjection of dopamine in a dose of 100 µg inhibited motor responses, lengthened latent periods and the reaction time of alternative choice tasks to 5-11 sec (normal 1-3 sec), but the actual decision connected with selective discrimination of the essential features of the stimuli carrying generalized information remained above the random response criterion (60%; $P < 0.05$; Fig. 1A, b). An increase in the dose of dopamine to 150 µg led to disturbance of the generalization function. The animals' behavior was marked by hypokinesia and inhibition. The responses became adequate more than 1 h later (Fig. 1B, b).

Evaluation of the results of investigation of alternative choice in intact animals after systemic injection of haloperidol showed a marked disturbance of comparison, discrimination, and generalization of the leading features of the signal during observations lasting more than 24 h (Fig. 1A, B, d). The mean percentage of correct solutions was 31 (70 in the control ex-

*Corresponding Member, Academy of Medical Sciences of the USSR.

Laboratory of Morphophysiology of the Conditioned Reflex, Brain Institute, Academy of Medical Sciences of the USSR, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 94, No. 8, pp. 37-39, August, 1982. Original article submitted February 12, 1982.

0007-4888/82/9408-1053$07.50

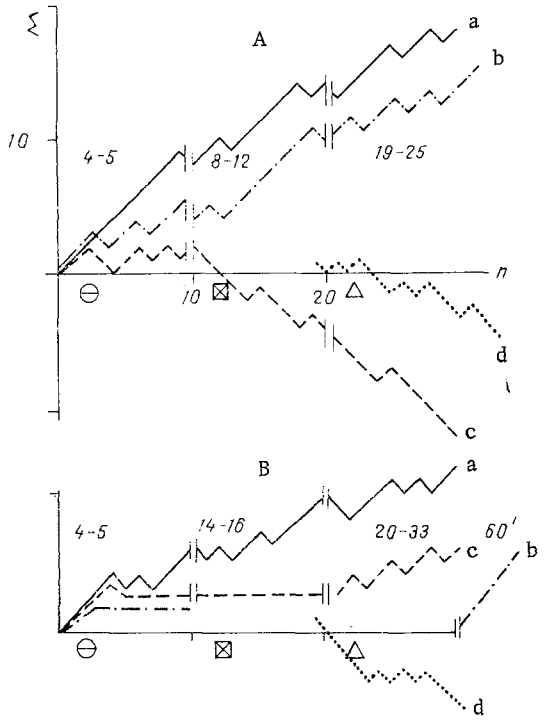

Fig. 1

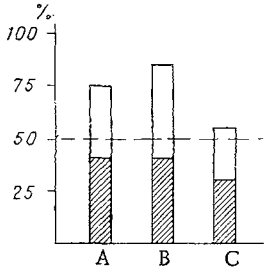

Fig. 2

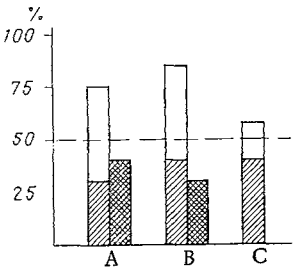

Fig. 3

Fig. 1. Time course of problem solving in generalization (A, B — different versions) after microinjection of atropine (a), dopamine (b), and neostigmine (c) into caudate nuclei and after systemic injection of haloperidol (d). Cumulation curve: each correct solution represented by upward slope at 45°, no solution — horizontal line. Abscissa, number of problems with geometric figures presented (n); ordinate, sum of correct responses (Σ). Numbers on graph indicate minutes after injection of drug.

Fig. 2. Effect of haloperidol 48 h after systemic injection into lobectomized (A), caudatectomized (B), and lobectomized and caudatectomized (C) cats. Shaded columns denote % of correct solutions of generalization problems by animals undergoing operations before receiving drug, unshaded columns denote increase in % of correct responses after receiving drug (difference significant, $P < 0.01$).

Fig. 3. Effect of haloperidol 30 min after systemic injection into lobectomized (A), caudatectomized (B), and caudatectomized and lobectomized (C) cats. Unshaded columns denote % of correct solutions of generalization problems in period of compensation in animals undergoing operation before receiving drug; obliquely shaded columns denote % of correct responses after receiving drug (difference significant, $P < 0.01$); cross-hatched columns denote % of correct responses after additional caudatectomy (A) and lobectomy (B).

periments, differences significant, $P < 0.01$).

Neuropharmacologic action on the cholinergic structures of the brain after systemic injection of atropine (or scopolamine) made no significant difference to the solution of generalization problems before and after injection of these drugs (the number of adequate responses in both cases varied from 60 to 70%; $P < 0.01$). Haloperidol, which blocks postsynaptic dopamine receptors, had a significant effect, for instance, on the mechanism of elementary reasoning activity in the animals. The results of the next group of experiments supported this view. After extirpation of the frontal cortex, the animals were unable to solve difficult generalization problems (Fig. 2A). Cats undergoing the operation solved problems in feature generalization statistically significantly in the course of 1-5 days 24-48 h after a single intraperitoneal injection of haloperidol (Fig. 2A).

If the lobectomized animals were taught to solve generalization problems up to a level in excess of random evasion (over 50%) in the period of compensation and recovery, haloperidol abolished the compensatory effect immediately after injection, as also did additional caudatectomy (Fig. 3A). The percentage of successful solutions did not exceed 30-40 in both cases ($P < 0.01$) and the solution time increased to 12 sec. A similar situation was found in the caudatectomized cats. Destruction of the head of the caudate nucleus caused disturbances of response to simple stimuli (Fig. 2B). After restoration of ability to generalize stimuli, inhibition of the dopaminergic system by parenteral injection of haloperidol (likewise an additional operation on the frontal cortex of these animals) led to decompensation again (Fig. 3B). Partial recovery of the lost functions could be achieved through training in cats undergoing both lobectomy and caudatectomy, but blocking of the "reserve" dopaminergic brain structures by injection of haloperidol completely abolished the previous compensatory effect (Fig. 3C). However, 24 h after injection of the drug a "rebound" effect was observed, namely, compensatory solving of the generalization problem (Fig. 2C).

Inactivation of the cholinergic neurotransmitter system by atropine (or scopolamine) caused no significant changes in the generalization response of animals undergoing the operations, whether in the decompensation or the compensation period: the percentage of correct responses remained below and above 50, respectively ($P < 0.01$).

An organic lesion of the caudate nucleus thus disturbs generalization function. Activation of the nigro-striatal dopaminergic system inhibits unit activity in the caudate nucleus (functional blocking of the striatum) [3]. However, optimal doses of dopamine in the present investigations caused no significant disturbances of intellectual operations (although relatively high doses appreciably altered behavior), since the frontal cortex evidently compensates hypofunction of the corpus striatum (this was shown by additional ablation of the frontal cortex [1]), whereas after blocking of the whole system of dopamine reception by haloperidol, there was no compensatory effect. The cholinergic system, the antagonist of dopaminergic transmission [6], inhibits it when neostigmine is injected into the caudate nucleus, and as a result the generalization function is disturbed, for cholinolytics in the present experiments caused no such pathological deviations. Meanwhile, when dopamine receptors were inhibited in animals undergoing operation a "rebound effect" was observed (i.e., compensation of the disturbances). evidently as a result of optimization of the reserve capacity of the dopaminergic structures.

It can be concluded from the facts described above that individual formations of the fronto-striatal integration system can provide reserve capacity for the restoration of neurodynamic processes such as discrimination, abstraction, and generalization of the essential features of signal stimuli. One of the probable ways by which neurochemical interaction takes place between the frontal cortex and caudate nucleus in the realization of goal-directed voluntary activity, based on heuristically detectable principles of operation with empirical rules, is connected with the dopaminergic neurotransmitter system; cholinergic mechanisms evidently modulate the fine balance between inhibition and excitation in this system.

LITERATURE CITED

1. O. S. Adrianov, Adv. Physiol. Sci., 17, 219 (1981).
2. O. S. Adrianov, L. N. Molodkina, E. I. Mukhin (E. J. Mukhin), et al., Acta Neurobiol. Exp., 40, 729 (1980).
3. E. B. Arushanyan and V. A. Otellin, The Caudate Nucleus [in Russian], Leningrad (1976).
4. R. R. Lideman, G. P. Zlobina, and A. G. Mukhin, Zh. Nevropatol. Psikhiat., No. 5, 762 (1980).
5. E. I. Mukhin, Zh. Vyssh. Nerv. Deyat., No. 6, 1181 (1980).
6. Y. Agid, P. Guyenet, J. Glevinski, et al., Brain Res., 86, 488 (1975).
7. D. Van Kammen, Psychoneuroendocrinology, 4, 37 (1979).