EFFECT OF CLOZAPINE ON BEHAVIORAL AND ELECTROGRAPHIC INDICES OF THE RESTRAINING FUNCTION OF THE CAUDATE NUCLEUS IN CATS

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Clozapine, in increasing doses (1-5 mg/kg), induced behavioral depression and inhibition of amphetamine-induced stereotyped behavior in unrestrained cats, accompanied by marked autonomic changes. Like chlorpromazine, clozapine enhanced the behavioral (the restraining of movement response) and electrographic (cortical spindle waves) indices of the restraining function of the caudate nucleus. The restraining response was more clearly affected by stimulation of the ventral zones of the head of the nucleus. Clozapine also abolished the weakening of caudate responses induced by stereotype-forming doses of amphetamine.

KEY WORDS: *clozapine; amphetamine-induced sterotyped behavior; restraining response; cortical spindle waves; caudate nucleus.*

According to some data the antipsychotic effect of neuroleptics may depend on blockade of dopamine receptors in nigro-striatal synapses and subsequent liberation of the restraining mechanisms of the caudate nucleus [1]. Among the other evidence in support of this hypothesis, correlation has been found between strengths of the antipsychotic action of drugs and their ability to induce side effects in the form of parkinsonism.

In recent years, however, this view has been questioned. The new neuroleptic clozapine (Leponex) has appeared, which rarely induces extrapyramidal disorders, which are regarded as an indicator of striatal hyperactivity. Since these are more often absent, it has been concluded that the drug has no dopaminolytic properties and that activation of the nucleus does not determine the antipsychotic effect not only of this, but also of other neuroleptics [9].

Meanwhile, previous observations [4] showed that the ability of chlorpromazine and haloperidol to enhance some indices of activity of the caudate nucleus during its low-frequency stimulation in cats is directly dependent on the strength of the antipsychotic action of these drugs. It was therefore decided to study the sensitivity of caudate phenomena to clozapine and also, by the use of this model, to determine the character of its relationship with amphetamine. The inhibitory effect of amphetamine on functions of the nucleus is considered to be an important source of the psychotic disorders in poisoning with this drug [1].

EXPERIMENTAL METHODS

Altogether 80 experiments were carried out on 22 cats of both sexes weighing 2-3.5 kg. Bipolar stimulating electrodes were first inserted into the head of the caudate nucleus and steel needles were inserted into the sensomotor cortex to record the EEG. Behavioral changes under the influence of the drugs were assessed visually and cyclographically [5]. Thresholds of the movement restraining response and of cortical spindle waves were recorded during low-frequency stimulation of the caudate nucleus [2, 6]. The drugs for investigation were injected intraperitoneally. Clozapine was provided by the firm of Hofman–La Roche (Switzerland).

EXPERIMENTAL RESULTS

In a dose of 0.5 mg/kg clozapine had no significant effect on the animals' spontaneous behavior. With an increase in the dose to 1 mg/kg a distinct tranquilizing effect took place with very slight limitations of locomotion or, less frequently, a drowsy state. After 2.5

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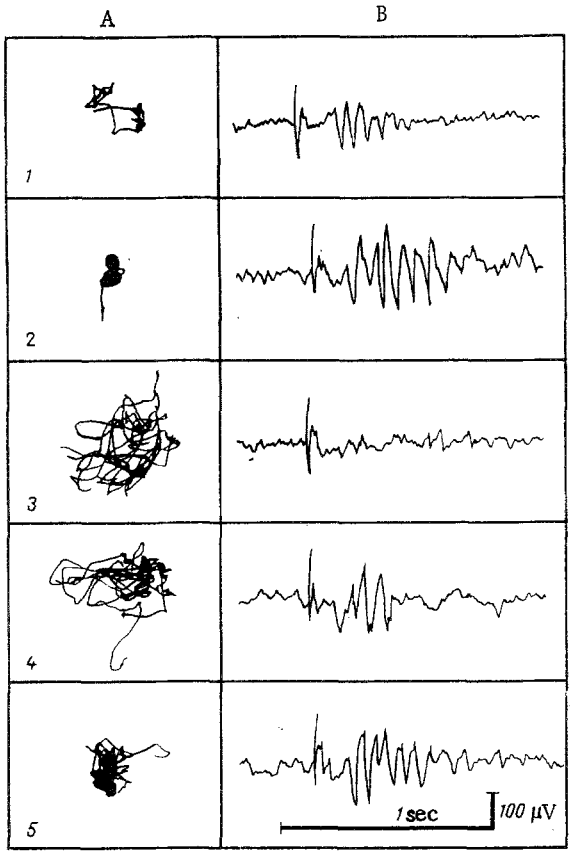

Fig. 1. Effect of clozapine on amphetamine-induced sterotyped behavior (A) and caudate spindle waves in cortex (B). 1) Normal conditions; 2) injection of 5 mg/kg clozapine; 3) after 1.5 mg/kg amphetamine; 4) injection of clozapine (2.5 mg/kg) against background of stereotyped behavior induced by amphetamine; 5) additional injection of 2.5 mg/kg clozapine. 1-2 and 3-5) Results obtained on different days of experiment.

mg/kg of the neuroleptic the sedation increased and the response to external stimuli was reduced. The gait became distinctive: During walking the posterior half of the trunk swung from side to side. Subsequent cumulation of the drug (up to 5 mg/kg) potentiated these phenomena, and this was accompanied by an increase in the automatic disturbances (progressive salivation, tachycardia, tachypnea, less frequently involuntary defecation). After repeated injections (at intervals of 2-3 days for 1-2 weeks) tolerance to clozapine was observed in only one animal.

Chlorpromazine taken for comparison in the same doses, modified the cats' behavior somewhat differently. It inhibited spontaneous and goal-directed locomotion and responses to external stimuli sooner and more strongly. Unlike clozapine, chlorpromazine lowered muscle tone and this was accompanied by less pronounced autonomic changes.

Clozapine modified sterotyped behavior induced by large (1-2.5 mg/kg) doses of amphetamine. With an increase in the dose of the neuroleptic the amplitude and assortment of stereotyped movements became progressively limited (Fig. 1A). Only short rotations of the head remained, accompanied by sharply increased salivation and by more rapid respiration and heart beat.

In the opposite combination, namely injection of amphetamine after the maximal (5 mg/kg) dose of clozapine, the same relationship was observed. Amphetamine induced stereotyped behavior, but in higher doses than in the control, namely 2-5 mg/kg. Furthermore, the character of the stereotyped behavior was changed in half of the animals. The amplitude of the automatic movements was reduced, and they were occasionally interrupted by short periods of inactivity. The sniffing observed previously disappeared from the pattern of this stereotyped behavior and the grooming was sharply reduced. Antagonism between chlorpromazine and amphetamine was more clearly two-directional in character, with complete abolition followed by restoration of the stereotyped movements.

Low-frequency (2 and 10 Hz) stimulation of the head of the caudate nucleus induced restraint of spontaneous and goal-directed movements, with a catatonic increase in muscle tone [3]. Clozapine potentiated this response. This was reflected in a progressive decrease in its threshold during cumulation of the drug. The averaged data for all the animals showed that the shift was statistically significant after a dose of clozapine of 2.5 mg/kg. It is interesting to note that subsequent cumulation of the neuroleptic caused no further increase

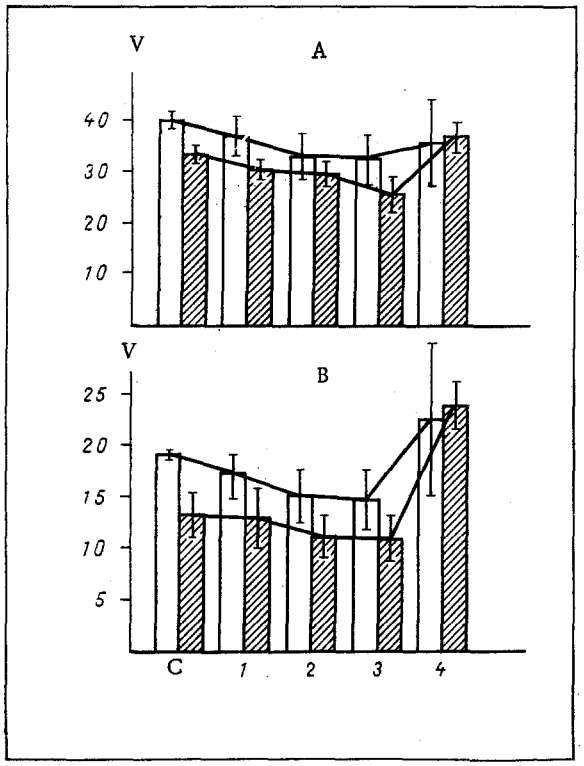

Fig. 2. Comparative effect of increase in doses of clozapine and chlorpromazine and of a combination of them with amphetamine on threshold of movement restraining response (A, in volts) and of spindle waves (B) during low-frequency (2 Hz) stimulation of caudate nucleus. Unshaded columns) effect of clozapine (mean results of 12 experiments on 2 cats), shaded columns) action of chlorpromazine (14 experiments on 4 cats). C) Control values of thresholds of response; 1, 2, 3) after injection of 1, 2.5, and 5 mg/kg of drugs respectively; 4) after their injection preceded by amphetamine in dose inducing stereotyped behavior.

in its effect (Fig. 2). In two cats it actually weakened the effect regularly in repeated experiments.

Simultaneously with lowering of the threshold, an increase in the intensity of the restraining response was observed. Whereas before injection of the neuroleptic it was estimated at 1-2 points, after the neuroleptic this increased to 3-4 points.

Chlorpromazine similarly potentiated the restraining function of the caudate nucleus. Its action, like the effect to clozapine, was abolished by injection of amphetamine, but only in doses which restored stereotyped behavior (Fig. 2).

Caudate restraint, induced from different parts of the nucleus, differs in its sensitivity of pharmacological agents. With this in mind, in repeated experiments on an animal (cat No. 5) with a multiple electrode in the head of the caudate nucleus, so that responses to dorsal, central, and ventral regions could be studied consecutively, the character of the effects of clozapine was determined. Like other neuroleptics, it was found to increase considerably the responses induced from the ventrolateral zones of the nucleus. A sufficiently stable shift was thus observed with effect from 0.5 mg/kg of the drug; admittedly, the effect was more stable during cumulation of clozapine (Fig. 3).

Meanwhile the neuroleptic facilitated the formation of caudate synchronized responses in the cortex. Single stimulation of the nucleus evoked bursts of spindle waves in the sensomotor area, in the form of a series (4-8) of high-amplitude slow waves. Under the influence of clozapine, against the background of EEG synchronization the threshold of their onset was lowered (Fig. 2), and in cases when the original response was insufficiently well marked, the duration and amplitude of the caudate spindle were increased (Fig. 1B). The lowering of the threshold of the EEG response increased in degree with an increase in the dose of the drug. According to this criterion clozapine surpassed chlorpromazine, which, although it also caused synchronization of the original EEG, facilitated the generation of spindle waves less strongly.

These observations agree with those of Stille, who showed in experiments on rats that clozapine prolongs caudate spindles and facilitates their appearance although, admittedly, only in high doses (10 mg/kg).

Amphetamine blocked the caudate response in the cortex. Its inhibitory effect was unblocked by increasing doses of clozapine (Fig. 2B). In some cases, moreover, the morphology of these restored waves differed somewhat from the initial pattern (Fig. 1B).

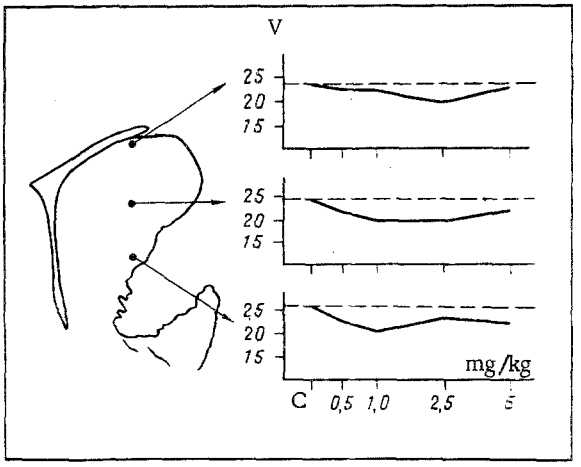

Fig. 3. Effect of clozapine on thresholds of caudate restraining response during stimulaion of different parts of head of caudate nucleus (2 Hz) in same animal (cat No. 5). Scheme on left shows location of electrodes from which corresponding response was obtained. Abscissa on graphs) doses of clozapine (in mg/kg); ordinate) absolute values of thresholds of restraining response (in V); broken line indicates original level.

Besides behavioral and EEG indices of the restraining function of the caudate nucleus, the effect of clozapine also was studied on the circular response to high-frequency (30 Hz) brain stimulation. Most frequently this was expressed as rotation of the animal's head to the side contralateral to stimulation. The threshold of these movements increased after administration of clozapine, but the change was significant only with a dose of 5 mg/kg. Chlorpromazine did not affect this behavioral phenomenon. According to the results obtained, in its ability to influence the activity of the caudate nucleus, clozapine is equal in all respects to the classical neuroleptics. Like chlorpromazine and haloperidol [4, 6, 8], it potentiates caudate restraining of movements and the accompanying spindle waves in the cortex and weakens the intensity of amphetamine-induced stereotyped behavior. These phenomena can be completely explained on the basis of the dopaminolytic properties of the drug. In fact, like other neuroleptics, clozapine increases the dopamine turnover in the corpus striatum [13], blocks striatal adenylate cyclase [11], and restores the rhythmic activity of nigrostriatal neurons when inhibited by amphetamine.

It is reasonable to interpret its inhibitory effect on the amphetamine-induced stereotyped behavior and its antagonism with amphetamine on the model of caudate responses from the same standpoints. These conclusions are, admittedly, not supported by the results of observations on rats indicating the absence of antiamphetamine and antiapomorphine effects of clozapine [9], possibly as a result of differences in species sensitivity of the animals, and also of the fact that, unlike in the present experiments, large doses of amphetamine, above the threshold for stereotyped behavior, were used. In rats also, intrastriatal injection of clozapine blocks amphetamine-induced stereotyped behavior [10].

All these facts, taken as a whole, run contrary to attempts to regard the properties of clozapine as a trump card to play against arguments for the leading role of the dopaminolytic effect in the process of the abolition of psychoses and the dopamine concept of schizophrenia [9]. The information obtained should rather be regarded as further confirmation in support of the writers' view that the caudate nucleus is the leading structure in the unraveling of certain forms of psychopathology [3]. Nevertheless, it must be recognized that they do not provide the answer to the question of the cause of the low intensity of the extrapyramidal phenomena during the treatment of schizophrenics with clozapine. This cannot be explained by assuming that the substance possesses cholinolytic properties [12], for their appearance is accompanied by weakening of the caudate restraining response [4]. The cause may perhaps lie in differences in sensitivity of the nigro-striatal and meso-limbic dopaminergic synapses to clozapine [8]. It must, incidentally, be pointed out that clinicians are by no means unanimous in their opinion of the side effects of clozapine. According to some observations, when it is used extrapyramidal disorders are found relatively frequently, although they are less severe and shorter in duration [7].

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