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The Stereotyped Behavior Syndrome: A New Model and Proposed Therapy

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KRYZHANOVSKY, G. N. AND M. N. ALIEV. *The stereotyped behavior syndrome: A new model and proposed therapy.* PHARMAC. BIOCHEM. BEHAV. **14**(3) 273–281, 1981.—The stereotyped behavior syndrome was induced in rats through local impairment of inhibitory GABA-ergic mechanisms in both caudate nuclei by bilateral microinjection of tetanus toxin, penicillin, or picrotoxin into the rostral part of the caudate nucleus. Intraperitoneally injected haloperidol suppressed the syndrome; this effect was dose-dependent. The same effect on the tetanus toxin-induced stereotyped behavior was produced by GABA microinjected bilaterally into the rostral part of the caudate nucleus of unrestrained rats. It was found in this model of tetanus toxin-induced stereotyped behavior that lithium chloride and diazepam can suppress the syndrome. Combined application of lithium chloride, diazepam, and haloperidol in minimal effective doses resulted in a much more complete and longer-lasting suppression of the syndrome than the separate use of these drugs. This effect is attributed to the joint specific actions of the drugs on pathogenetically interrelated components of a hyperactive determinant structure that arises in the caudate nuclei after impairment of the GABA control and that is responsible for the stereotyped behavior syndrome.

Stereotyped behavior syndrome Determinant structure Caudate nucleus GABA Haloperidol Diazepam Lithium Combined specific therapy

THE stereotyped behavior syndrome has been considered as an experimental model equivalent to certain psychoses [27, 40, 44]. The elucidation of the mechanisms of this syndrome and the development of its models and therapy are therefore topics of current interest. The underlying cause of the stereotyped behavior syndrome is hyperactivation of the dopamine system of the neostriatum [18, 27, 40, 44], and the existing pharmacological models of the syndrome rely on the use of dopamine agonists [18, 21, 22, 24]. The principal drawback of most such models is that pharmacological preparations are introduced systemically and so may have widespread effects on various parts of the central nervous system (CNS), which makes it difficult to identify the pathogenetic target structure, although it has been shown that the syndrome can be induced by microinjection of dopamine into the caudate nuclei [18,21]. Also, these models represent the terminal event of a pathological process, namely hyperactivity of the dopamine system, and fail to provide an answer to the question why this hyperactivity occurs under natural conditions. Yet this question has to be answered if the pathogenesis of psychoses is to be understood.

We have approached the problem from the standpoint of our concept regarding the role of hyperactive determinant structures in pathological conditions of the CNS [30–32]. According to this concept, when inhibitory mechanisms are locally impaired, the disinhibited structures become overactive and begin to determine the behavior of the respective parts of the CNS. We have termed such structures "hyperactive determinants". At their basis may be either disinhibited systems of mediator secretion or generators of pathologically enhanced excitation that are formed by populations of disinhibited neurons [31,32]. Hyperactive determinant structures transform physiological systems into pathological ones, and the clinical expressions of the behaviors of these pathological systems are particular neuropathological syndromes. This concept constituted the basis for our studies on experimental simulation of various neuropathological syndromes by causing hyperactive determinant structures to form in specific parts of the CNS [1, 30–36]. In the study reported here, we generated hyperactivity in the caudate nuclei by tetanus toxin (TT) which we also employed in developing other models [30–36]. Our experience shows that TT may be regarded as a universal tool for creating hyperactive determinant structures and simulating the corresponding syndromes [30–36], because this toxin can impair various kinds of inhibition [6, 10, 12, 15, 29, 45] and bring about sustained effects. This enables one to follow the development of a syndrome in unrestrained animals. Bilateral microinjection of TT into the rostral part of the caudate nucleus was found to result in a complex of syndromes, the first of which was the stereotyped behavior syndrome. This syndrome then passed into a catatonia succeeded in some animals by parkinsonism; moreover, a choreiform hyperkinesia or myoclonia was seen in a number of cases [33–36].

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Injection of TT into only one caudate nucleus led to a characteristic rotational behavior syndrome similar to the one observed to occur when the dopaminergic nigro-striatal system was acted upon unilaterally [46]. The present paper describes the stereotyped behavior syndrome created by microinjection of TT into both caudate nuclei and suggests a novel type of therapy for that syndrome. For comparative purposes, in separate experiments we used picrotoxin and penicillin, both of which are known to impair the GABA-induced inhibition [13, 14, 15].

METHOD

Noninbred male white rats weighing 200–300 g were used. TT was injected stereotaxically, bilaterally, in doses of 1–3 MLD for rats per injection ($0.2 \cdot 10^{-4}$ to $0.15 \cdot 10^{-3}$ ml) by means of a glass micropipet with a tip 20–30 μm in diameter. GABA (0.2 M), benzylpenicillin sodium (20 IU), and picrotoxin ($6 \cdot 10^{-5}$ M) were each injected in a volume of up to 6 μl at a rate of 1 μl/min into each caudate nucleus through a cannula implanted previously. The site of injection corresponded to coordinates AP −2.0, L 2.5, and H 4.0 of a stereotaxic atlas [19]. The implanatation of the cannulas and the microinjection of TT were performed under hexobarbital anesthesia (150 mg/kg intraperitoneally). After this surgical procedure each rat was kept in a separate cage. Stereotyped behavior was assessed both visually and by recording motor activity by means of an actograph, a device that consisted of a cage of organic glass measuring 40 × 40 × 40 cm, the bottom of which rested on rubber shock-absorbers and was rigidly connected to a seismic detector whose data were plotted an an actogram by an automatic ink-writer on paper tape. Visual observations were noted on the actogram directly. The effects of the test drugs were assessed using the following scale of ratings: 0 — absence of behavioral and locomotor responses; 1 — locomotor responses only; 2 — long-continued masticatory movements; 3 — searching movements of the head; 4 — searching movements accompanied by intensive sniffing of the interior of the cage; 5 — licking and gnawing of the cage bottom and walls. The results of each experiment were presented as histograms where the degree of stereotypy (using the ratings given above) was plotted on the ordinate and the time (in minutes) during which particular manifestations of stereotypy were evident was plotted on the abscissa. The magnitude of effect produced by the drugs was determined by calculating an efficacy index (EI) from the formula $(S_1 - S_2) \cdot T$, where S_1 is the baseline (maximal) intensity of stereotyped behavior corresponding to rating 5, S_2 is the stereotyped behavior after injection of a given drug, and T is the time (in minutes) during which the S_2 was observed.

Each systemically applied drug and each control solution was injected in 0.25 ml of a 0.9% NaCl solution. In control experiments, neither the microinjection of TT inactivated by an appropriate dose of antitoxin nor the implantation of intracerebral cannulas had a significant effect on the behavior of rats. In experiments with intracerebral injections of drugs, an isotonic NaCl solution injected in the same volume as the drug and shown to have no effect on stereotyped behavior was used as control. In experiments with intraperitoneal injection of haloperidol, the control was the solvent injected by the same route.

RESULTS

Signs of stereotypy appeared usually 12–18 hr after injection of TT bilaterally into the rostral part of the caudate nucleus. These signs occurred either periodically as repetitive bursts of stereotyped behavior or as continuous stereotyped manifestations, sometimes going on for several hours. The syndrome consisted of a set of regularly repeated movements, including short to-and-fro runs or walks along the wall of the cage, shifting from one forelimb to the other in rapid succession, searching movements of the head with intensive sniffing of the interior of the cage, gnawing and licking of the cage bottom, and masticatory movements. These signs were the same as those seen in pharmacologically induced stereotyped behavior [18, 21, 22, 40].

Effects of Haloperidol

Haloperidol blocks dopamine receptors [2, 20, 23], which explains the effects it produces in experimental and clinical disorders of the CNS, including psychoses. In our model of the stereotyped behavior syndrome, haloperidol at 2.5 to 5.0 mg/kg completely blocked the syndrome (Fig. 1). With 1 mg/kg haloperidol, stereotyped behavior was suppressed incompletely: stereotyped responses just decreased in frequency and intensity. The dose of 0.2 mg/kg (Figs. 3, C; 5, II; and 6, II) had no effect on stereotyped behavior in 2 rats and weakened it (to rating 4) for a short time (30.6 ± 17.9 min) in 3 rats. The changes in stereotyped behavior were characterized by an alternation of short periods when stereotypy decreased only slightly (to rating 4) with those during which the syndrome was blocked completely. The mean value of the EI with the dose of 0.2 mg/kg was 17.3 ± 8.9.

These experiments with haloperidol show that an essential pathogenetic component of the stereotyped behavior syndrome model under discussion is hyperactivation of the dopamine system of the neostriatum: blockade of the dopamine receptors by haloperidol abolished the syndrome, this effect being dose-dependent. This result agrees with those of other investigations where the effect of haloperidol on stereotyped behavior was studied [20,23].

Effects of GABA

GABA plays an important part in the regulation of the function of the striatum and of dopamine secretion in this nucleus by nigro-striatal neuron terminals [4,26]. Since TT can impair GABA-ergic inhibitory mechanisms by blocking the release of the mediator from presynaptic terminals [6, 10, 12, 15, 29, 45], impairment of GABA control may be thought to underlie the disinhibition of dopamine secretion in the caudate nuclei. Accordingly, in order to restore this control, we microinjected GABA via cannulas into both nuclei of unrestrained rats (Fig. 2). This procedure was found to block stereotyped behavior of the animals. The effect was evident as soon as during the injection of GABA. The first to be reduced was locomotor activity: stereotyped runs and walks became less frequent and less regular. Then, the shifting from one forelimb to the other ceased, as did the sniffing, licking, and gnawing activities. Bursts of masticatory movements persisted for some time to disappear also. Grooming activity was seen to appear in some rats. The duration of GABA action varied from 10 to 40 min and depended on the dose and on the severity of the stereotypy syndrome. Reappearance of the signs of stereotyped behavior occurred in an order inverse to that of their disappearance.

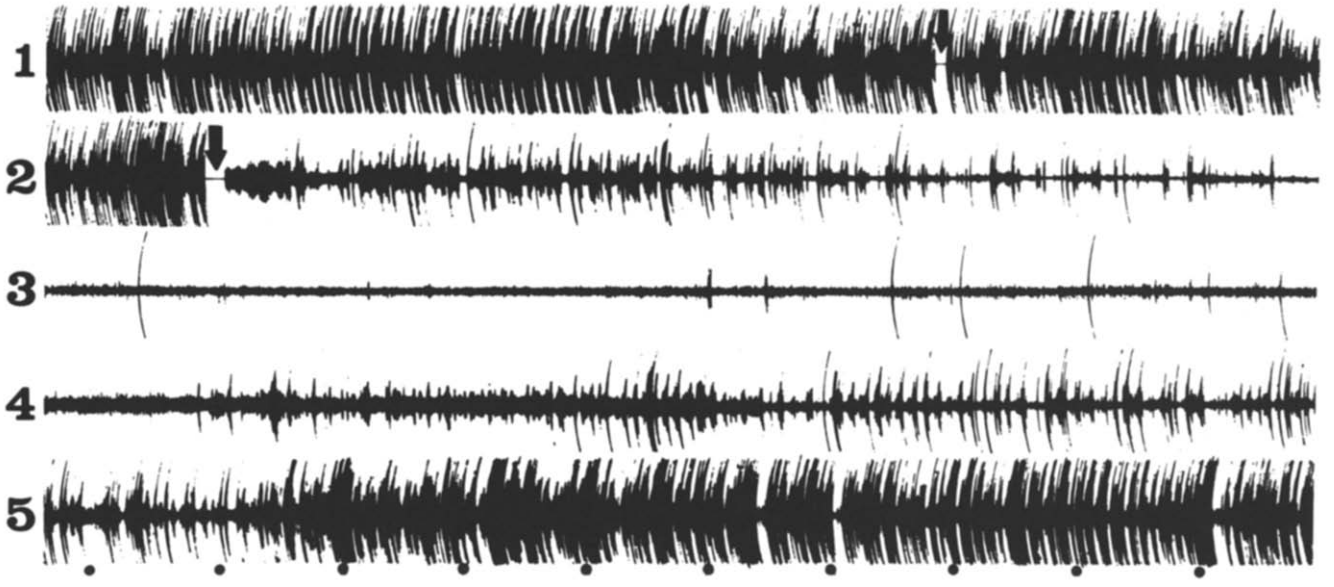

FIG. 1. Effect of haloperidol on stereotyped behavior of a rat. (1) Actogram of stereotyped behavior before and after intraperitoneal injection of control solution; (2) progressive decreases in frequency and intensity of stereotyped manifestations after intraperitoneal injection of haloperidol (2.5 mg/kg); (3) no stereotyped behavior 15–20 min after haloperidol injection; (4 and 5) recovery of stereotyped behavior 95–105 and 125–135 min postinjection, respectively. The time marker here and in Figs. 2 to 4 is 1 min. In all figures, except Fig. 2, arrows indicate the moment of injection.

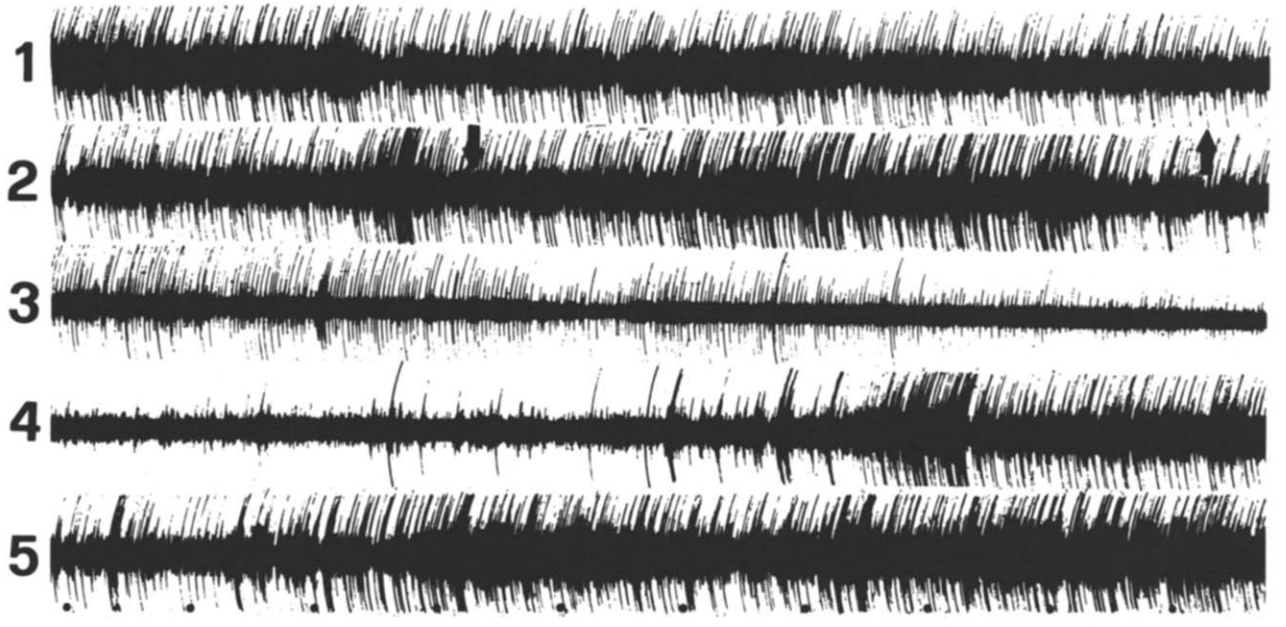

FIG. 2. Effect of GABA microinjected bilaterally into rostral part of caudate nucleus, on stereotyped behavior of a rat. (1) Actogram of stereotyped behavior before GABA injection (6 μl of 0.2 M solution at the rate of 1 μl/min); (2) same but during GABA injection (arrows indicate the beginning and end of injection); (3) 1–10 min after injection, showing progressive suppression of stereotyped behavior; (4 and 5) recovery of stereotyped behavior 20–30 and 30–40 min postinjection, respectively.

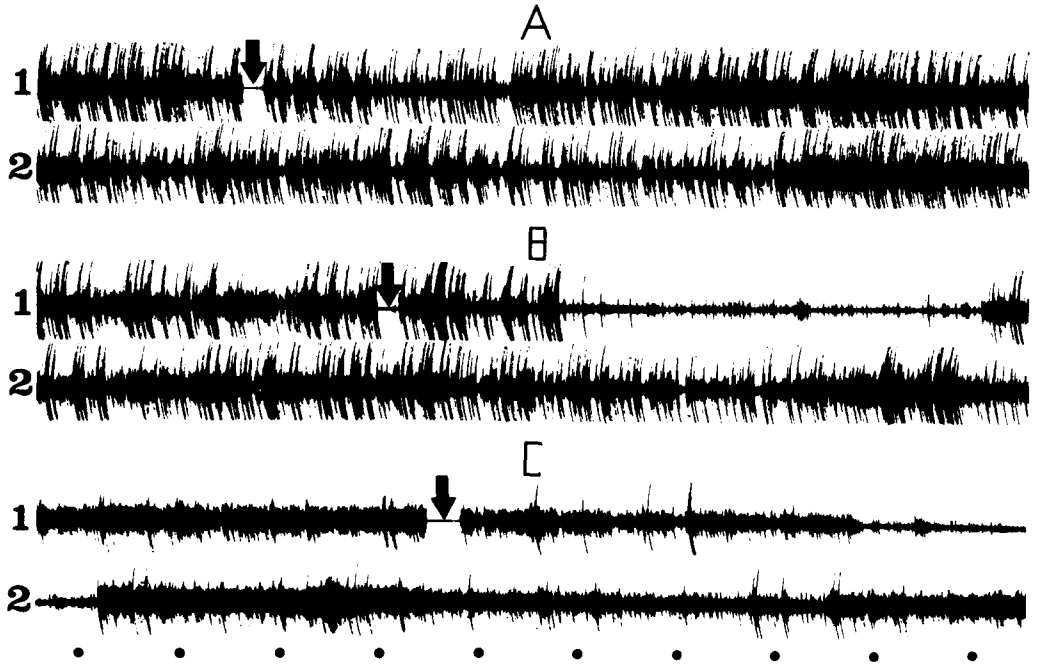

FIG. 3. Effect of lithium chloride at 50 mg/kg (A), of diazepam at 0.1 mg/kg (B), and of haloperidol at 0.2 mg/kg (C) applied separately, on stereotyped behavior of rats. (A) Short-term decrease in intensity of stereotyped behavior at 1–4 min and 11–14 min postinjection. (B) Progressive attenuation of stereotyped behavior and enhancement of locomotor activity after injection, followed by short-term suppression of the syndrome and its subsequent recovery with slightly diminished intensity of its manifestations at 11–16 min. (C) Reduction in intensity of stereotyped behavior after injection, followed by suppression of the syndrome at 5–6 min and its recovery with slightly diminished intensity of its manifestations at 10–14 min.

Effects of Penicillin and Picrotoxin

These drugs were used as agents that disrupt the GABA-induced inhibition [11, 13, 14]. Either of them injected bilaterally into the rostral part of the caudate nucleus resulted in a characteristic stereotypy syndrome with all its items described above. The first signs appeared as soon as during injection and the syndrome lasted for 1.2 to 1.8 hr. Its striking feature was that it was of a clearly defined paroxysmal nature. The paroxysms included variously manifested items of stereotyped behavior. Some animals showed exaggerated grooming of their muzzles and some showed hyperkinetic manifestations.

Haloperidol at 1 mg/kg abolished the syndrome elicited by penicillin or picrotoxin. Intrastriatal microinjections of GABA failed to suppress this model of the syndrome. The present experiments support the view that the GABA control of the neostriatum must be disrupted for the dopamine system of the nuclei to become disinhibited and for stereotypy to arise.

Effects of Diazepam

It has been demonstrated that benzodiazepines activate the GABA-ergic apparatus and that this effect is brought about at the synapsis level by several mechanisms [17, 25, 28, 37]. There is also evidence to show that diazepam blocks the picrotoxin-induced *in vivo* release of dopamine in the cat caudate nucleus [7]. In view of this we have studied the effect of diazepam on the stereotyped behavior syndrome model described here. In doses of 1 and 2 mg/kg diazepam suppressed stereotyped behavior 3.5–5.0 and 1.2–2.0 min postinjection, respectively; recovery of the syndrome occurred after 1.0–2.5 and 3.0–4.5 hr [36]. A noteworthy feature of diazepam action was that as well as suppressing stereotyped manifestations (intense searching movements, sniffing, licking, gnawing, etc.), diazepam caused, just after injection, a short-term enhancement of locomotor activity: the number and speed of runs and walks increased. The magnitude and duration of this effect were dose-dependent. With 2 mg/kg diazepam there occurred a brief but considerable enhancement of locomotor activity followed by its complete disappearance. The dose of 0.1 mg/kg (Figs. 3, B; 5, III; and 6, III) caused attenuation of stereotyped behavior in 9 of the 10 test rats; in addition, 4 rats displayed enhanced locomotor activity during 10.2 ± 2.4 min. The degree of suppression of the syndrome varied widely: the EI ranged from 6.0 to 149.0 (mean value=29.5 ± 15.3); the mean duration of diazepam action was 13.1 ± 1.2 min. The effect from diazepam became evident just after injection and took the form either of a short-term attenuation of stereotyped behavior to rating 2–4 (in 5 rats) or a sharp diminution of the syndrome from rating 3 or 4 to 0, followed by a rapid return to the baseline status.

Effects of Lithium

The mechanisms of lithium action are many and varied

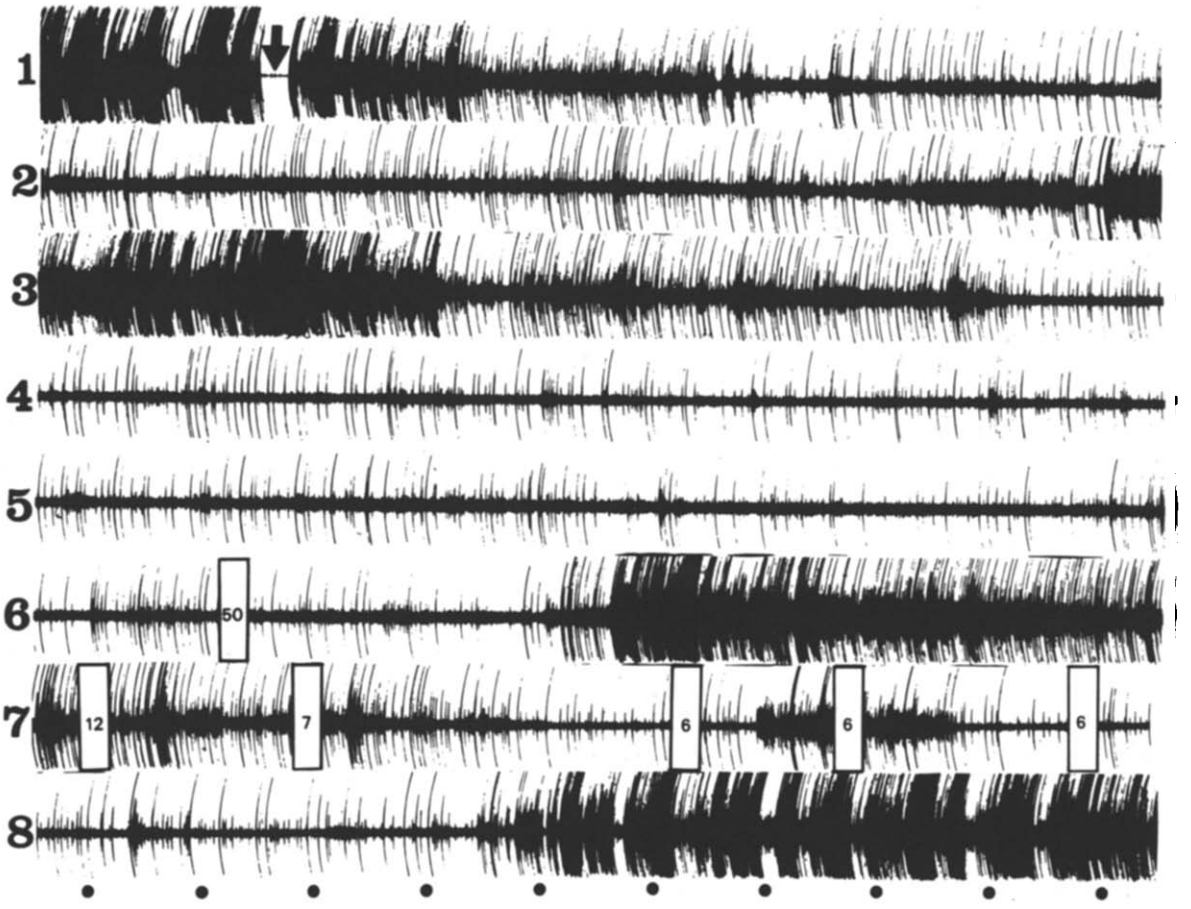

FIG. 4. Effect of lithium chloride, diazepam, and haloperidol applied jointly in the same doses as in Fig. 3, on stereotyped behavior of a rat. (1) Before intraperitoneal injection of the drugs; (1–8) after injection. (1 and 2) Progressive attenuation of stereotyped behavior after injection with subsequent complete suppression of the syndrome during 12 min; (2 and 3) burst of stereotyped behavior followed by its progressive attenuation; (3 to 6) this syndrome completely suppressed during 70 min; (6 and 7) alternation of periods of complete absence of stereotyped behavior with those during which the syndrome is manifested to varying degrees; (8) recovery of stereotyped behavior by 170th min. Numbers within boxes indicate the time (minutes) during which stereotyped manifestations were similar to those prior to and after the indicated time interval.

[42]. Apart from its ability to pass across membranes by making use of sodium channels and by inhibiting the entry of Ca during action potentials [41], lithium depresses the brain adenyl cyclase [16], prevents dopamine receptors from becoming super-sensitive [38], stimulates intraneuronal breakdown of catecholamines, diminishes the release of transmitters, and increases their re-uptake [5, 8, 39, 43]. These properties of lithium have led us to test its effects on the stereotypy syndrome model under consideration.

Lithium chloride injected intraperitoneally had a pronounced dose-dependent depressor effect on stereotyped behavior of rats [36]. In a dose of 500 mg/kg, it suppressed stereotyped behavior and locomotor activity completely and very rapidly (virtually at the tip of the needle, as it were); recovery of the syndrome occurred 3 to 8 hr postinjection. A dose of 250 mg/kg completely suppressed stereotyped movements of the head as well as licking and gnawing activities, but had a smaller effect on locomotor manifestations such as walks and runs; the action of lithium chloride persisted for 1.0 to 2.5 hr. With 125 mg/kg lithium, stereotyped behavior was suppressed partially. The dose of 50 mg/kg (Figs. 3, A; 5, I; and 6, I) had varying effects. Thus, of the 10 test rats, stereotyped behavior remained unchanged in 2 and was suppressed for a short time to rating 3 (with occasional bursts of stereotypy of rating 4 or 5) in 6; the EI was 19.6 ± 4.1 and the effect lasted 29.5 ± 10.7 min. In 2 rats with marked elements of licking, lithium caused bursts of gnawing activity during the first few minutes postinjection while in 5 rats a short-term suppression of stereotyped behavior was accompanied by decreases in general locomotor components of behavior.

Effects of Diazepam plus Haloperidol

Combined application of diazepam at 0.1 mg/kg and haloperidol at 0.2 mg/kg (Figs. 5, V and 6, IV) had a pronounced

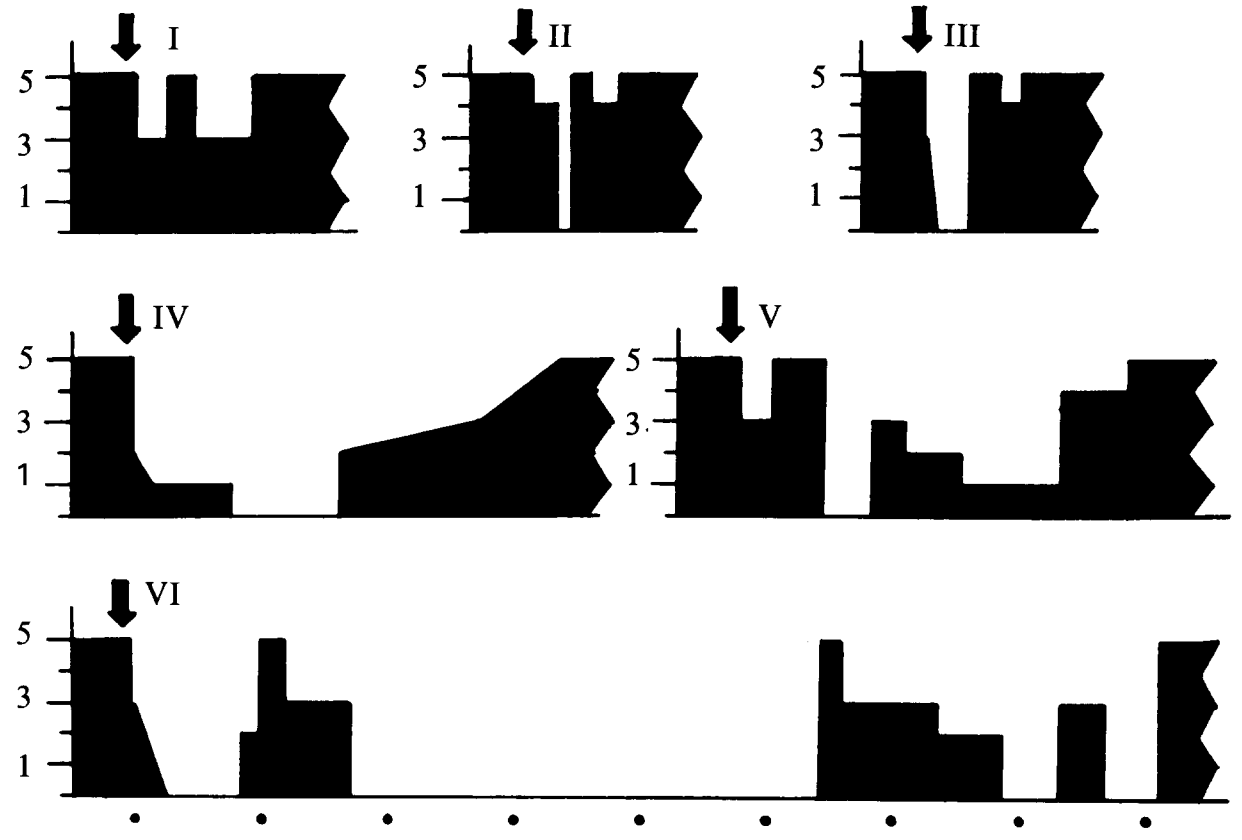

FIG. 5. Effects of lithium chloride, diazepam, and haloperidol applied separately or in various combinations (same doses as in Fig. 3), on stereotyped behavior of rats. (I) Lithium chloride; (II) haloperidol; (III) diazepam; (IV) lithium choride + diazepam; (V) diazepam + haloperidol; (VI) lithium chloride + diazepam + haloperidol. Data of a single experiment for each drug and combination. Abscissa, time (minutes); time marker=20 min.

depressor effect on stereotyped behavior: the EI was equal to 169.1 ± 5.3 and the effect lasted 72.0 ± 4.6 min. Patterns of stereotyped behavior inhibition were similar in all animals. Periods of attenuated stereotyped behavior alternated with those during which behavioral and motor activities were completely absent.

Effects of Diazepam plus Lithium

Diazepam at 0.1 mg/kg plus lithium chloride at 50 mg/kg (Figs. 5, IV and 6, V) strongly weakened stereotyped behavior in all 8 rats; the EI was 232.0 ± 52.19 and the duration of effect was 76.5 ± 4.9 min. The responses were varied. The most often repeated response was an alternation of periods of attenuated stereotyped behavior with those when stereotyped behavior was completely absent. A noteworthy feature was that periods of complete suppression were longer than in the case of jointly acting diazepam and haloperidol.

Effects of Diazepam plus Lithium plus Haloperidol

A combination of these three drugs had the most pronounced blocking effect on the stereotyped behavior syndrome (Figs. 4; 5, VI; and 6, VI). The effects lasted longer (166.2 ± 29.7 min on the average) and the EI was much higher (575.0 ± 65.3 on the average). In general, this combination caused complete suppression of stereotyped behavior preceded by a short (2–5 min) period of latency during which the syndrome was suppressed partially. The periods when stereotyped behavior was absent were much longer than such periods in the experiments described above.

DISCUSSION

The results of this study warrant some conclusions and suggestions.

The stereotyped behavior syndrome can serve as a good illustration of our concept that neuropathological syndromes are clinical expressions of the activities of the corresponding pathological systems [30–32]. In this particular case the pathological system was induced by a hyperactive determinant structure located in the caudate nuclei.

It is evident from the foregoing that impairment of the GABA-ergic inhibitory control in the rostral part of the caudate nuclei is an essential pathogenetic mechanism of the stereotyped behavior syndrome. Impairment of this control (by tetanus toxin, picrotoxin, or penicillin) leads to hypersecretion of dopamine. Restoration of the GABA-ergic control

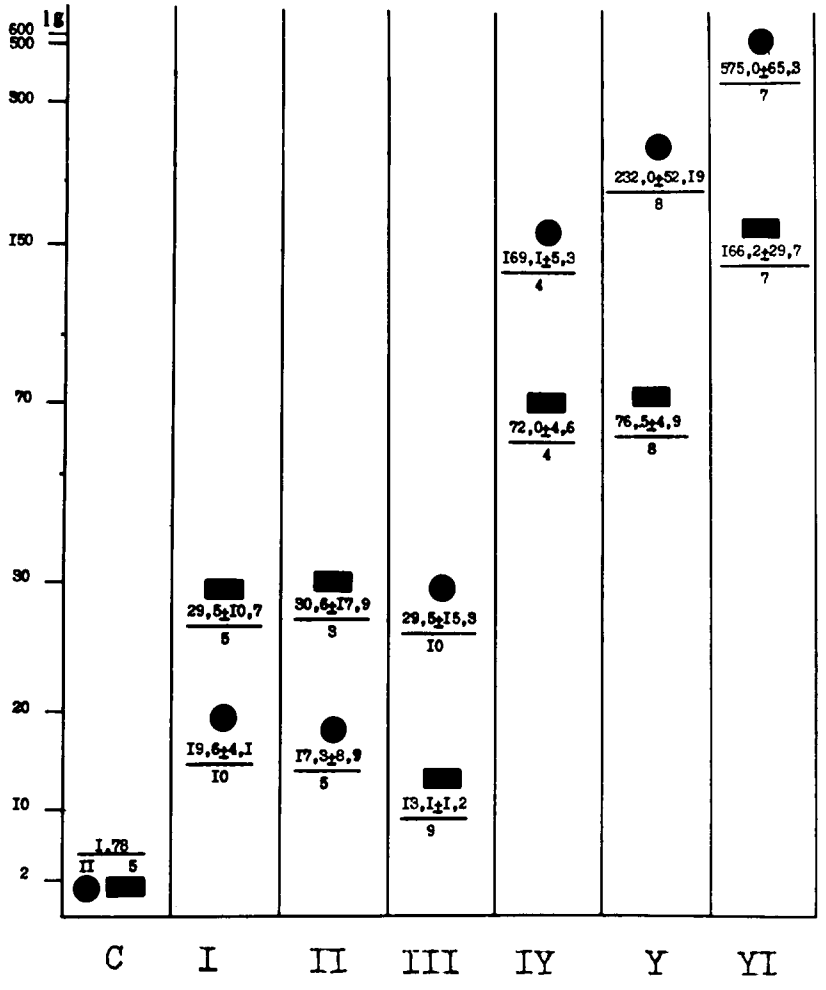

FIG. 6. Effects of lithium chloride, diazepam, haloperidol, and their combinations (same doses as in Fig. 3), on stereotyped behavior of rats. (C) Control (injection of physiological saline); (I) lithium chloride; (II) haloperidol; (III) diazepam; (IV) haloperidol + diazepam; (V) diazepam + lithium chloride; (VI) lithium chloride + diazepam + haloperidol. ●, efficacy index; ▬, duration of effect (minutes). Figures above horizontal lines denote mean durations of effect (minutes) or mean efficacy indices and those below these lines denote numbers of rats.

normalizes dopamine secretion, and this causes suppression of the syndrome.

The pathogenesis of the stereotyped behavior syndrome may therefore be viewed as a chain process comprising the following events: (1) impairment of the GABA-induced inhibitory control of dopamine secretion from terminals of dopaminergic neurons of the substantia nigra ending in the caudate nuclei; (2) disinhibition of the dopamine system of the caudate nuclei and hyperactivation of this system; and (3) inhibition of cholinergic neurons of the caudate nuclei as the result of this hyperactivation [1, 3, 9, 20–24, 27, 40].

These conclusions are consistent with the finding that exogenous GABA is not always effective in the presence of stereotyped behavior syndrome: it is effective only when the GABA receptors of the caudate nuclei are not blocked (as in the case of TT administration) and is ineffective when they are blocked (as they are in the case of penicillin or picrotoxin administration). Hence one may infer that the mechanism of action of the drugs used should be compatible with the pathogenetic structure of the syndrome, in particular with the neurochemical nature of the key pathogenetic components of the determinant part of the pathological system involved. This conclusion may be thought to be valid also for other neuropathological syndromes and to explain to some extent why the same drug may have different effects in syndromes that appear to be identical in their clinical manifestations.

The elucidation of the mechanisms of the stereotyped behavior syndrome described here and, in particular, the identification of the pathogenetic components of its hyperactive

determinant structure makes it logical to pose the question of instituting a therapy that would involve a set of influences on the pathogenetically interrelated components of the determinant structure. The present investigation has indicated that a combined specific pathogenetic therapy should ensure a highly effective suppression of the syndrome and that this result can be achieved by using each drug in a lower dose which by itself has a relatively small effect. Each drug in the combination acts specifically on particular pathogenetic components of the hyperactive determinant structure (thus, diazepam acts on the GABA-ergic apparatus; haloperidol, on dopamine receptors; and lithium, on the presynaptic dopamine system), but, since the components of that structure are interrelated, a true potentiation of their effects results.

Moreover, the drugs used in this study may have relatively selective actions on components of the determinant as compared to their actions on chemically similar structures in other parts of the CNS. Thus, the effects of lithium and diazepam are more manifest under conditions where the state of neuronal membranes and the reactivity of neural structures, including neuronal populations, are altered.

Since the stereotyped behavior syndrome is pathogenetically similar to certain forms of psychosis, the proposed combined specific pathogenetic therapy may be expected to be effective also in some other related disorders of the brain.

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