EFFECT OF LEPTAZOL ON BACKGROUND ACTIVITY OF SINGLE CORTICAL UNITS AND THEIR RESPONSES TO STIMULATION OF THE CAUDATE NUCLEUS

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Leptazol (5-10 mg/kg, intravenously) produced biphasic changes in the single unit responses of the sensorimotor cortex of unanesthetized cats to stimulation of the caudate nucleus at different frequencies. During the first 1-2 min after injection, strengthening of caudate inhibition and depression of facilitatory responses were observed. At the same time, the frequency of background unit activity was increased. At the 3rd-4th minute of recording, the inhibitory responses, however, were weakened. The initial intensification of caudate inhibition is probably the result of elevation of the arterial pressure due to leptazol.

One cause of the excitatory action of certain analeptics on the central nervous system is a disturbance of the function of inhibitory mechanisms. A structure which effectively depresses various cortical functions is the caudate nucleus [6-8].

It was therefore decided to study the effect of a stimulant (leptazol) on inhibitory caudato-cortical relationships. The writers' previous investigations [1, 4] showed that leptazol produces biphasic changes over a period of time in central inhibitory and facilitatory single unit responses in the spinal cord. With this in mind, in the present investigation its effect was assessed in detail at different times after injection.

EXPERIMENTAL

Experiments were carried out on unanesthetized cats. After brief inhalation of ether the animal was fixed to a frame, transferred to artificial respiration, and curarized. Bipolar nichrome electrodes (thickness 100 μ, interpolar distance 0.5 mm) were inserted into the caudate nucleus stereotaxically in accordance with the coordinates of the atlas of the cat's brain. Square pulses (0.5-100/sec, 1 msec, 5-15 V) were used for stimulation. Single unit activity in the sensorimotor cortex was recorded extracellularly by means of capillary microelectrodes filled with 4 M NaCl solution. After amplification, the potentials were recorded on film by a loop oscillograph. To identify sensorimotor units, antidromic stimulation was applied to the pyramidal tract at the level of the bulbar pyramids, and repetitive photic and acoustic stimuli also were used.

The blood pressure in the femoral artery was recorded throughout the experiment. Leptazol (0.5 solution, doses of 5-10 mg/kg) was injected intravenously, slowly. The criterion of inhibition or facilitation of cortical units was the difference between the frequency of spike activity during and before brain stimulation.

EXPERIMENTAL RESULTS

Activity of 113 sensorimotor cortical units was studied; in 18 of them, activity was studied in detail after injection of leptazol. Most cells, to judge from their stable response to pyramidal tract stimulation,

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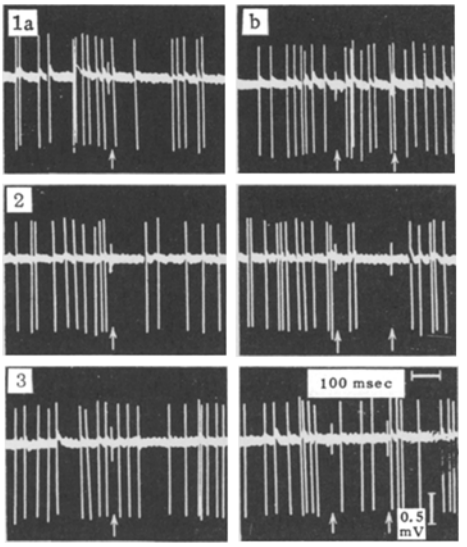

Fig. 1

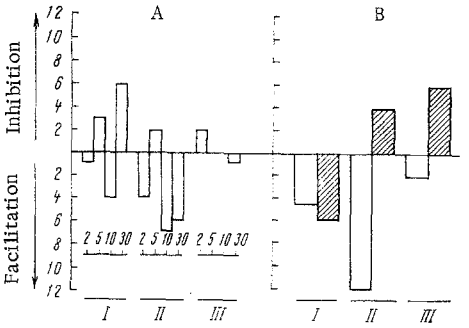

Fig. 2

Fig. 1. Changes in caudate responses of somatosensory cortical unit at different times after injection of leptazol. Inhibition of background activity during stimulation of caudate nucleus at 2/sec (a) and facilitation of discharges of some neuron during stimulation at 5/sec (b). 1) Normal; 2) 1 min after injection of 10 mg/kg leptazol; 3) 4 min after injection. Arrows denote artifacts of stimulation.

Fig. 2. Effect of leptazol on inhibition and facilitation of cortical units during stimulation of caudate nucleus. A) Single unit responses to different frequencies of stimulation (numbers beneath columns) at various times after injection of 5 mg/kg leptazol; B) aggregated dynamics of changes in inhibitory effect (results obtained in 12 units) during stimulation at 2/sec, when action of drug was accompanied by a pressor response (unshaded column), and in absence of pressor response (data for 6 units; shaded column). Vertical axis: difference between frequency of background activity and evoked response (spikes/sec) of cortical neurons. I) Normal; II) 1-2 min; III) 3-5 min after injection of leptazol.

can be classified as pyramidal cells. They were located mainly at a depth of between 900 and 2100 μ.

Most of the studied neurons were characterized by irregular, or occasionally grouped background activity. The firing rate varied over a wide range (from 3 to 30 spikes/sec), with a mean value of 10/sec.

The initial activity varied differently throughout the period of action of leptazol. Immediately after injection (0.5-2 min) it increased slightly (to 13/sec). At the same time, in some cases a tendency toward grouping of the spikes were observed. The slower the initial rhythm, the greater the increase in firing rate, but only up to a certain limit. On the other hand, in the case of 4 units whose background activity exceeded 20/sec, the firing rate became slower. A similar phenomenon was observed by the writers during analysis of the activity of spinal interneurons [3].

Later, toward 3-4 min of recording and thereafter until the end of the leptazol effect, the normal background activity was restored. Slowing and quickening of the firing rate was observed in about equal numbers of cells. The mean rate thus remained the same as before.

Various behavioral and electrographic manifestations are known to correspond to different frequencies of stimulation of the caudate nucleus [2, 6, 10]. At a slow rate (1-10/sec) these are mainly inhibitory in nature, while at a faster rate (30/sec or above) responses of excitatory type have been described. In the present investigation a wide range of frequencies (from 0.5 to 100/sec) was studied. According to the results, cortical unit responses to different parameters of stimulation were extremely variable. Only in a few cases were they uniform in direction, and most frequently inhibitory and facilitatory effects were mixed even after a very small change of frequency (for example, from 2 to 5/sec). Inhibition of background activity occurred most constantly when frequencies of stimulation of 2 and 10/sec were used.

Inhibitory caudato-cortical responses showed biphasic changes after injection of leptazol at a moderate speed (3 mg/kg/min). Initially (1-2 min after injection) they showed a marked increase. This was reflected in a greater slowing of spike activity and prolongation of the inhibitory pauses immediately after application of the stimulus (Fig. 1a). For a time, in the first phase, a definite inhibitory effect could be obtained in certain units, despite the fact that normally this was absent. The strengthening of inhibition cannot be attributed to a simple increase in frequency of background unit activity, which was observed to take place at that time, for usually not only was the difference between the frequencies of the initial and evoked activity increased, but the absolute magnitude of the actual response also was reduced.

Strengthening of the inhibitory influence of the caudate nucleus was combined as a rule with simultaneous blocking of the facilitatory responses, which could be observed in the same unit when a different frequency of stimulation was used. Caudate facilitation of background activity was weakened, disappeared completely, or was replaced by inhibition (Fig. 1b). Responses of a neuron reacting by inhibition to stimulation at 2 and 10/sec, and by facilitation to stimulation at 5 and 30/sec are shown in Fig. 2A. Initially after injection of leptazol the inhibitory effect increased appreciably, while the facilitatory effect showed a parallel decrease, or even replacement by inhibition (at 30/sec).

A different picture was observed 3-4 min after injection and throughout the remainder (10-15 min) of the time of action of the analeptic. In this second phase, definite depression of the inhibitory responses developed. Not only were they abolished, but frequently they were replaced by an increase in the firing rate (Fig. 2A). The aggregated data are shown in Fig. 2B. The degree of facilitation could also be reduced or slightly increased by comparison with its initial level. This last effect was observed most frequently after injection of 10 mg/kg leptazol, and was more characteristic of high (30 and 100/sec) frequencies of stimulation. Facilitation was strengthened both during stimulation of the caudate nucleus and after its discontinuation (as a "rebound"). Changes affecting facilitatory and inhibitory responses of caudate origin are thus predominantly coupled in character. This principle did not extend, however, to responses to acoustic and photic stimulation. A few of the tested units showed signs of polymodality. The quickening and depression of activity of these units in response to acoustical or photic stimuli varied independently of fluctuations in the responses to stimulation of the caudate nucleus.

The results show that leptazol produces biphasic changes in inhibitory influences of the striatum, weakening them for most of the time. Considering the importance of this structure as a mechanism for restraining cortical functions, including motor functions, it can be postulated that this effect plays an important role in the general pattern of the stimulant action of the drug.

The brief strengthening by leptazol of inhibition of cortical units is comparable with the analogous phenomenon which has been demonstrated in spinal cord cells [1, 4]. It is perhaps based on hemodynamic disturbances produced by the analeptic. This is confirmed by several arguments. Even at the slow rate at which the drug was injected, at the initial moment the arterial pressure rose (by 20-30 mm Hg). To exclude the effect of a pressor response on unit activity, in some cases the injection was given extremely slowly (0.5-1 mg/kg/min). It was found that if the blood pressure did not rise, the first phase of leptazol action was absent. Conversely, inhibition was weakened and was more constantly replaced by facilitation (Fig. 2B). Furthermore, when in control experiments pituitrin was given in doses to give an identical pressor effect (0.1 unit/kg), inhibitory responses to stimulation of the caudate nucleus were strengthened without a subsequent second phase.

A reflex from the baroreceptors can mobilize inhibitory zones of the recticular formation of the brain stem, which send impulses in both descending and ascending directions [11]. This can facilitate the strengthening or detection of the inhibitory striatal effects. The possibility is likewise not ruled out that the inhibitory system of the caudate nucleus may be activated spontaneously, strengthening reticular control over the cortex.

Intensification of the function of caudato-cortical inhibitory mechanisms in the first phase cannot easily be reconciled with the simultaneous increase in frequency of background unit activity. The increase in their excitability is evidently the result of the direct stimulant action of leptazol on the cortex [9]. Paroxysmal waves on the electrocorticogram, characteristic of this drug, appear 8-10 sec after its intravenous injection [5]. On the other hand, pituitrin, which strengthens the inhibition of single units of the maximum of elevation of the arterial pressure did not, according to the present observations, modify or reduce the frequency of the background discharges.

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