EFFECT OF LEPTAZOL ON INTERNEURON ACTIVITY OF THE SPINAL CORD

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Results are described showing the effect of leptazol on extracellularly recorded electrical activity of the spinal cord interneurons. Leptazol modifies spontaneous activity of the interneurons and their responses to afferent and supraspinal stimulation.

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Leptazol increases the amplitude of polysynaptic reflexes and polysynaptic potentials of single motoneurons of the spinal cord [2, 4]. It also influences the function of centrifugal pathways with complex organization [1, 5, 10]. Both effects may be dependent on changes in activity of the spinal interneurons.

We therefore decided to study the effect of leptazol on spontaneous activity of the interneurons and on their responses to afferent and supraspinal stimulation.

EXPERIMENTAL METHOD

Experiments were carried out on cats anesthetized with nembutal (30-40 mg/kg intraperitoneally 4-5 h before the experiment began). Potentials of single interneurons were recorded at the level of the lumbar segments of the spinal cord through extracellular capillary microelectrodes filled with 4 M NaCl. Dorsal and ventral roots, the motor cortex on both sides (in the region of the anterior sigmoid gyrus), and certain bulbar structure were stimulated. For bulbar stimulation thin bipolar electrodes were inserted into the brain stem through the cerebellum. The localization of the electrodes were determined histologically.

Leptazol (5-15 mg/kg) was injected intravaneously at a speed excluding the possibility of substantial fluctuations of arterial pressure. As a rule the pharmacological effect was assessed 2-3 min after injection.

The difference between the frequency of unit activity before and after stimulation was determined.

EXPERIMENTAL RESULTS

Altogether 34 interneurons located mainly in the posterior horns of the spinal cord were investigated. The frequency of spontaneous unit activity varied from 1-2 to 40/sec. Leptazol increased and decreased the frequency of spontaneous activity in equal numbers of cases, so that altogether the frequency remained unchanged at 11/sec. However, if all the cells taken before injection of the drug were arranged in order of increasing frequency of their spontaneous activity, the effect of leptazol was to increase the discharge of neurons with an initial frequency of 4-12/sec. As a rule no spontaneous activity appeared in "silent" cells, while in the case of a very low frequency of activity (not exceeding 4/sec), leptazol had no effect. In neurons with a higher frequency (more than 12/sec) of spontaneous activity, the frequency was slowed.

Leptazol had no significant effect on amplitude and duration of the group volley recorded from interneurons in response to a single-above-threshold stimulus applied to the dorsal root. In 8 of 15 neurons a tendency for the frequency of the discharge to increase was observed. The following general principle was established: the higher the initial frequency of the volley, the stronger the action of leptazol (coefficient of correlation $r = +0.62$; $P = 0.2$). In 6 cases, however, the group activity was inhibited. In the aggregate, therefore, the response of the neurons was not statistically significant (Fig. 1, 4). The multiple discharges of Renshaw's cells evoked by stimulation of the ventral root (Fig. 2, 1) likewise were unchanged. Facilitatory

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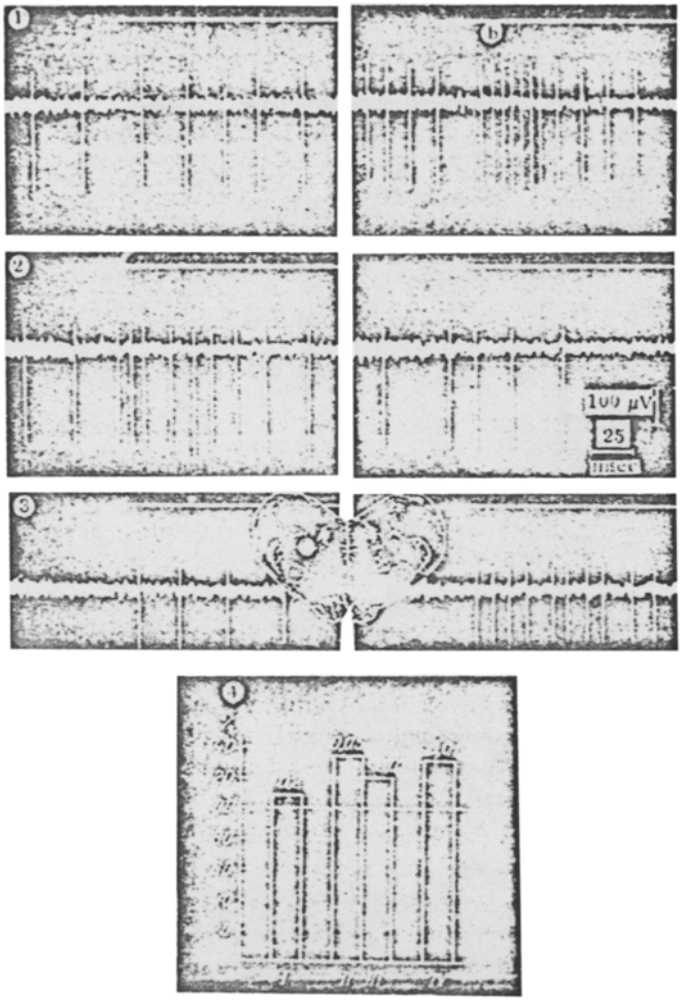

Fig. 1. Effect of leptazol on facilitation of spinal interneurons. 1) Increase in spontaneous activity during stimulation of contralateral motor cortex; 2) ipsilateral cortical facilitation; 3) activity of "silent" neuron in response to bulbar stimulation (location of electrode in medulla indicated on diagram); a) normal; b) after injection of 10 mg/kg leptazol; 4) mean value of facilitatory response after injection of drug, in percent of initial level; I) group discharge in response to afferent stimulation; II and III) facilitation from ipsilateral and contralateral motor areas respectively; IV) bulbar facilitation. Numbers above columns give values of P.

impulses from the contralateral motor cortex were mainly increased (on the average from 49 to 64/sec). This took place most constantly in cells whose spontaneous firing rate was above 10/sec (Fig. 1, 1). In 3 of 13 cases, slight depression of cortical facilitation was observed.

Leptazol was less regular in its effect on facilitation of the interneurons during stimulation of the ipsilateral motor cortex. An increase in suprasegmental responses was recorded in only half of the cells (in 4 of 8). In the rest they were inhibited (Fig. 1, 2) or undisturbed. In 8 of 11 cases leptazol increased bulbar facilitation (on the average from 46 to 62/sec; Fig. 1, 3). This result was observed during stimulation of structures differing in complexity of their organization and the character of their connections with the segmental apparatus of the spinal cord. Responses of some reticular nuclei (reticular parvocellular, reticular ventral) and descending tracts (reticulo- and vestibulospinal tracts) were increased equally. In 3 neurons (reticular gigantocellular nucleus) a decrease in the degree of facilitation was found.

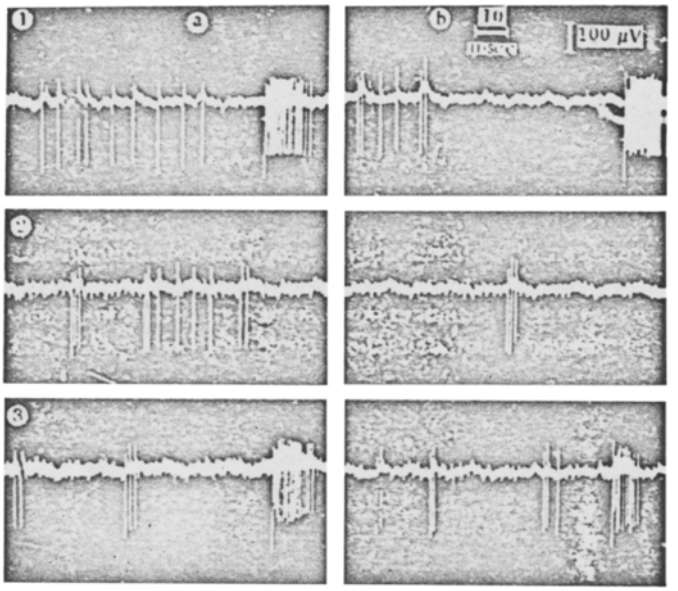

Fig. 2. Effect of leptazol on responses of Renshaw's cells. 1) Spontaneous and evoked unit activity; 2) spontaneous activity against a background of stimulation of contralateral motor cortex; 3) inhibition of evoked discharges against a background of stimulation of the reticular parvocellular nucleus; a) normal; b) after injection of leptazol (15 mg/kg).

Indices of cell activity of mainly segmental origin were relatively resistant to the action of leptazol. Meanwhile, facilitation of spontaneous activity during stimulation of various motor centers of the brain, according to our observations, increased distinctly. This is in agreement with the concept of the more selective action of leptazol on supraspinal regulation of spinal reflexes than on the reflexes themselves [3, 8].

The duration of the inhibitory pauses was regularly decreased by leptazol (Fig. 3, 1). This result was observed in 18 of 21 cases (a shortening on the average from 168 to 119 msec) and it did not depend on a simultaneous change in frequency of spontaneous activity of the neurons by the analeptic. Meanwhile a positive correlation was found between the initial duration of inhibition and the degree of its shortening by leptazol (coefficient of correlation $r = +0.64$; $P < 0.05$). Since the inhibitory pauses described in spinal animals were not so clearly apparent, and their weakening by leptazol was not associated with any simultaneous increase in group discharges, it can be assumed that suprasegmental structures played a definite role in the formation of the pauses.

Like facilitation, cortical inhibition of the interneurons differed in its sensitivity to the analeptic. The decrease in inhibition during stimulation of the contralateral motor cortex was more marked (on the average almost double the initial level). This effect was obtained in 6 of 7 cases, although the difference was not statistically significant (Fig. 3, 4). Weakening of inhibitory regulation took place at frequencies of spontaneous unit activity exceeding 10/sec, i.e., under conditions when the corresponding facilitatory responses were distinctly increased. Inhibitory influences of the ipsilateral motor cortex were less constantly disturbed. Their weakening was recorded in 4 of 8 neurons, irrespective of the frequency of spontaneous activity. In the other cases inhibition was actually increased.

Inhibition of spontaneous activity during stimulation of different bulbar structures on the whole showed a tendency to weaken under the influence of leptazol (Fig. 3, 3). Removal of inhibition was observed in 4 of 8 cells, and its inversion into facilitation was found twice. In 3 cases the magnitude of inhibition remained as before, while in one it increased. Pharmacologically resistant inhibitory influences originated from the reticular gigantocellular nucleus, but responses of the reticular ventrical nucleus and descending tract were suppressed.

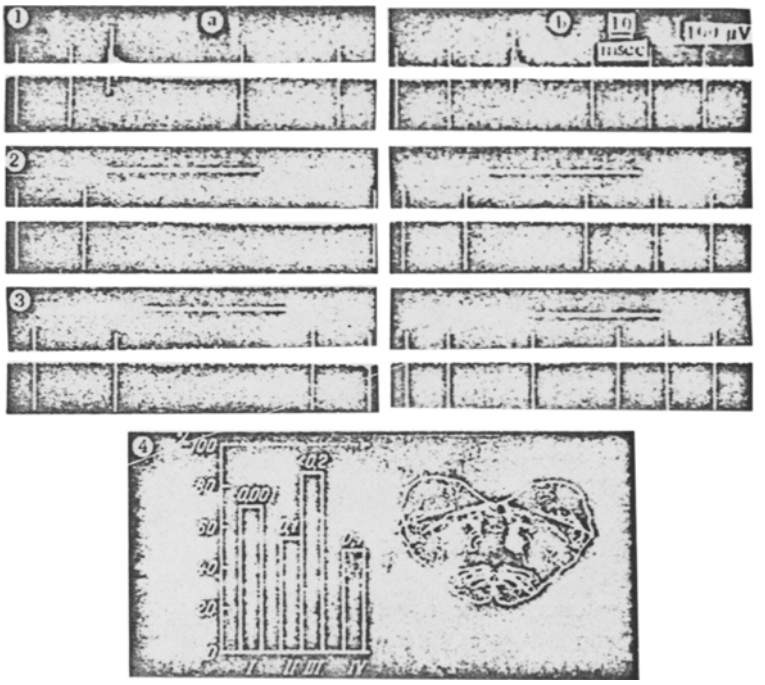

Fig. 3. Change in inhibitory responses of interneurons produced by leptazol. 1) Inhibitory pause in response to afferent stimulation; 2) inhibition of spontaneous activity during stimulation of contralateral motor cortex; 3) bulbar inhibition of the same neuron (localization of electrodes indicated on diagram). Oscillograms 2 and 3 taken from two parts of trace – beginning and end of stimulation (upper horizontal line is marker of brain stimulation); a) normal; b) after injection of leptazol (10 mg/kg); 4) mean magnitude of inhibitory effect after injection of leptazol (in percent of initial level): I) inhibitory pause; II and III) inhibition from ipsilateral and contralateral motor cortex respectively; IV) bulbar inhibition. Numbers above columns give values of P.

In three cases, when activity of the Renshaw's cells was recorded, although leptazol had no effect on the magnitude of the multiple discharge and slightly lowered the frequency of spontaneous activity, at the same time it strengthened suprasegmental inhibition of the spontaneous activity (Fig. 3, 2) and of the evoked responses (Fig. 3, 3). Our observations conflict with the view of Lewin and Esplin [9], who concluded from indirect evidence that leptazol ought to increase the function of the Renshaw's cells.

We can conclude from the results obtained by the study of interneurons of the posterior horns that in general leptazol weakens descending inhibition. Comparison of the overall results of its influence on positive or negative responses suggests that the action of the drug is evidently due primarily to an increase in the flow of facilitatory impulses to the interneurons, because we know that it has no effect on postsynaptic and presynaptic inhibitory mechanisms [6, 7]. Displacement of the equilibrium between the two types of descending influences in favor of facilitation may take place both at the segmental level and in the brain as a result of interaction between certain cerebral structures.

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