EFFECT OF LEPTAZOL, TROXIDONE, AND PHENYTOIN ON POSTSYNAPTIC POTENTIALS OF MOTONEURONS DURING SUPRASEGMENTAL STIMULATION

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Leptazol, troxidone and phenytoin had no significant effect on short-latency reticulospinal, vestibulospinal, and rubrospinal excitatory postsynaptic potentials, but effectively modified polysynaptic responses.

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Investigations of descending synaptic influences using a microelectrode technique have shown that several supraspinal centers are connected with the lumbar motoneurons in cats not only through complex multirelay polysnaptic pathways but also through simple mono- and disynaptic projections [2-4, 6, 8]. To obtain further details regarding the character of these supraspinal synaptic influences we investigated their sensitivity to pharmacological agents with stimulant and inhibitory action.

EXPERIMENTAL METHOD

Experiments were carried out on cats anesthetized lightly with Nembutal (30-40 mg/kg 5-6 h before recording began) and immobilized with flaxedil. Potentials of the lumbar motoneurons were recorded intracellularly by means of micropipets filled with 0.6 M K_2SO_4 solution. The ipsilateral reticular formation and vestibular nuclei and the contralateral red nucleus, together with other structures in the brain stem, were stimulated by means of bipolar electrodes with tips 50-80 μ in diameter and a distance of 0.3-0.1 mm between poles, introduced stereotaxically into the brain. The location of the tips of the electrodes was verified histologically in each experiment. Contact unipolar silver electrodes were used to stimulate the contralateral sensorimotor cortex. Single square pulses or short rhythmic series were applied for stimulation. The pulse duration was 0.1-0.5 msec and the strength of the current 0.1-0.8 mA (up to 2-3 mA for cortical stimulation). The drugs to be tested were injected intravenously at a rate not producing hemodynamic changes, as judged by the level of the blood pressure in the common carotid artery.

EXPERIMENTAL RESULTS

The action of leptazol pentamethylenetetrazole; 5-20 mg/kg) was studied on 18, and that of troxidone (trimethadione; 100-300 mg/kg) and phenytoin (diphenylhydantoin 10-30 mg/kg) on 16 α-motoneurons. For recording the responses of cells showing no essential signs of injury over a long period of time, the test drugs were reinjected.

TABLE 1. Effect of Leptazol on Excitatory and Inhibitory Polysynaptic Responses

Time of recording	Latent period (in msec)				Amplitude (in mV)				Duration (in msec)			
	EPSP	p	IPSP	p	EPSP	p	IPSP	p	EPSP	p	IPSP	p
Before injection	20,4		16,5		2,9		3,4		32		39	
1 min after	19,3	>0,05	11,0	<0,05	2,5	<0,05	4,3	<0,001	35	>0,05	58	<0,05
6 min after	14,9	<0,05	12,5	>0,05	4,7	<0,001	4,9	<0,02	45	<0,05	68	<0,01

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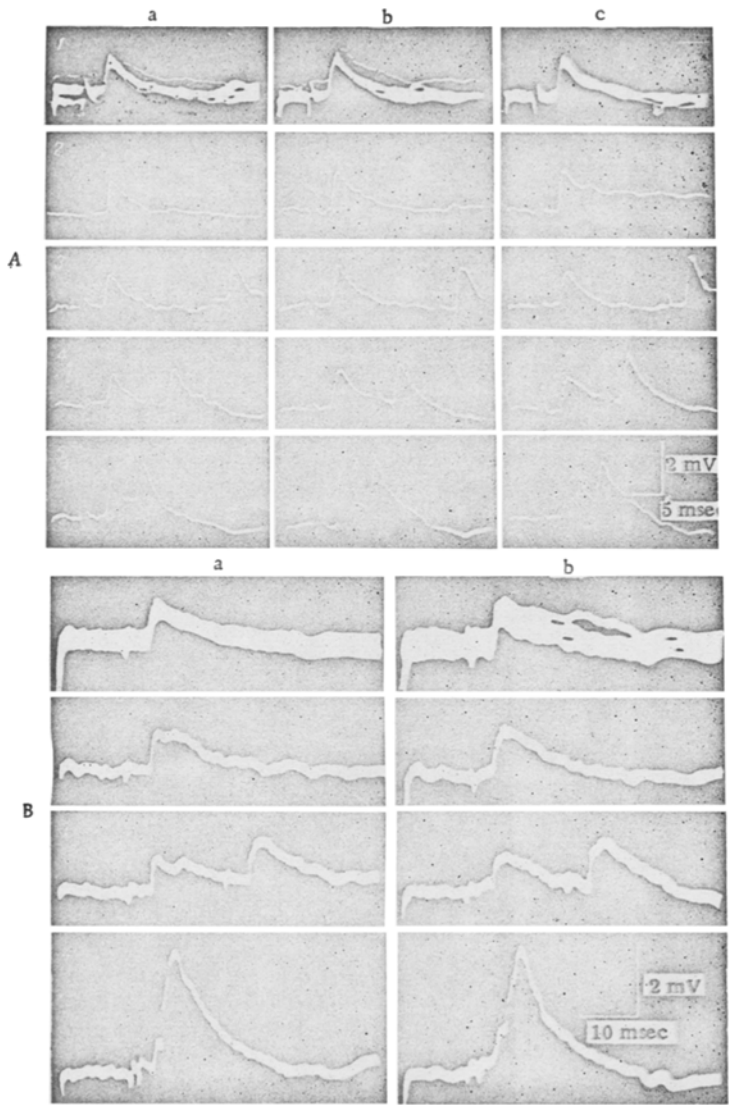

Fig. 1. Effect of leptazol (A) and troxidone (B) on short-latency vestibulospinal EPSP in response to single and paired stimuli. A) EPSP before (a) and 5 min after injection of 7.5 mg/kg leptazol (b), and 3 min after additional injection of 7.5 mg/kg leptazol (c); 1) repeated superposition of 10-15 paths; 2) single paths; 3-5) responses to paired stimuli; B) EPSP before (a) and 15 min after injection of 200 mg/kg troxidone (b); 1) repeated superposition of 10-15 paths; 2) single paths; 3-4) respones to paired stimuli.

The synaptic responses of the motoneurons were divided into two groups. One group consisted of excitatory postsynaptic potentials (EPSP) arising in response to single stimulation of the reticular formation of the medulla and pons, nuclei of the vestibular complex, and the red nucleus. These EPSP appeared after a very short (3-4 msec) latent period, and the interval between the arrival of the fastest components of the dorsal surface potential or the focal potential of the ventrolateral columns and the beginning of the EPSP demonstrated that at least the initial part of the EPSP is monosynaptic in nature [2, 3, 5]. Frequently the short-latency EPSP were simple in form, similar to monosynaptic potentials evoked by a volley in group IA muscle afferents. The inhibitory postsynaptic potentials (IPSP) and the EPSP arising only in response to rhythmic stimulation had a longer latent period (exceeding 5 msec) and were regarded as polysynaptic responses.

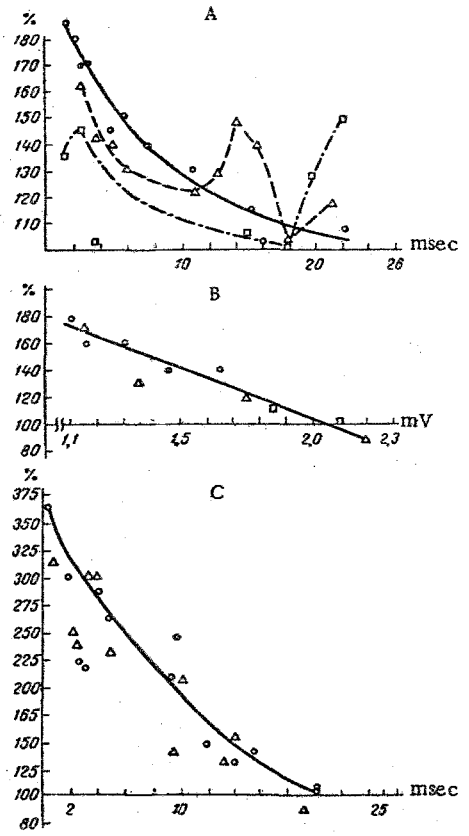

Fig. 2. Effect of leptazol (A, B) and troxidone (C) on potentiation of short-latency vestibulospinal EPSP during paired stimulation. A) Relationship between potentiation and interval between stimuli. Abscissa, interval (in msec); ordinate, amplitude of second response (in percent of first). Circles denote control measurements, triangles measurements after injection of 7.5 mg/kg leptazol, squares—after additional injection of 7.5 mg/kg leptazol. B) Relationship between degree of potentiation of second EPSP and amplitude of first. Abscissa, amplitude of first EPSP (in mV); ordinate, amplitude of second response (in % of first). Circles denote measurements before injection of leptazol, triangles and squares measurements after two injections of 7.5 mg/kg leptazol. C) Relationship between potentiation and interval between stimuli. Abscissa, interval (in msec); ordinate, magnitude of second response (in %). Circles denote control measurements; triangles denote measurements after injection of 200 mg/kg troxidone.

Leptazol had no effect on the latent period of the short-latency EPSP evoked by reticulospinal, vestibulospinal, or rubrospinal impulses. The amplitude of these potentials either remianed unchanged after injection of leptazol or increased slightly (Fig. 1A). Meanwhile, the descending phase of the EPSP was usually lengthened, and supplementary waves sometimes appeared on it.

In response to repeated stimulation the short-latency EPSP exhibit the characteristic property of potentiation in proportion to the decrease in the interval between stimuli [2, 3]. After injection of leptazol the potentiation of the second response persisted although the typical course of the relationship between the intensity of potentiation and the interval between stimuli was disturbed (Fig. 2A). This could have been due either to an increase in potentiation with long (10-20 msec) intervals between stimuli or to an increase in the amplitude and decrease in the stability of individual EPSP. A special analysis of the relationship between intensity of potentiation of the second response and amplitude of the first (with the interval between them constant) showed the presence of a distinct correlation between these two values, the corresponding measurements obtained before and after injection of leptazol lying approximately on one straight line (Fig. 2B). These facts confirm the hypothesis [3] that the potentiation of short-latency EPSP of suprasegmental origin is associated with the participation of an additional synaptic relay, probably on a proportional internuncial neuron.

Troxidone in doses of 100-300 mg/kg did not change the latent period of the short-latency EPSP and had no significant effect on their amplitude (Fig. 1B). In some cases, after injection of troxidone shortening of the descending phase of the EPSP was observed, and this was regarded as the result of suppression of components of the EPSP associated with the additional relays. The development of potentiation in response to paired stimuli was undisturbed by troxidone (Fig. 2C).

Postsynaptic potentials of polysynaptic nature revealed higher sensitivity to all the drugs tested. Polysynaptic EPSP were not all changed in the same manner by leptazol. Besides the simple increase in amplitude (Fig. 3A), in some cases a biphasic response was observed: an initial fall of amplitude in the first 1-3 min after injection was followed by an increase above the control level. In four cells distortion of the EPSP was observed under the influence of leptazol, i.e., conversion of a depolarization into a hyperpolarization response (Fig. 3B). The effect observed was undoubtedly due to the fact that the EPSP recorded in such experiments was in fact a mixed response, the inhibitory fraction of which was masked by algebraic summation of postsynaptic depolarization and hyperpolarization [2]. Consequently, the unequal influence of leptazol on the excitatory and inhibitory fractions of the postsynaptic potential must lead to distortion of the latter. In fact, leptazol possessed a marked

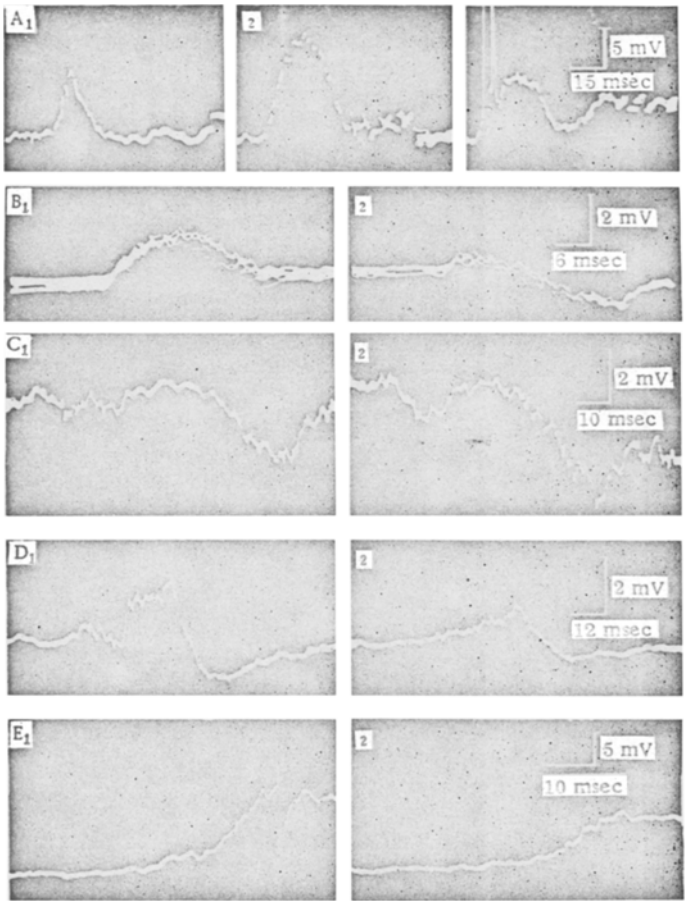

Fig. 3. Effect of leptazol, troxidone, and phenytoin on polysynaptic responses of motoneurons. A) Corticospinal EPSP before (1) and 1 min (2) and 17 min (3) after injection of 10 mg/kg leptazol; B) reticulospinal EPSP before (1) and 5 min after (2) injection of 5 mg/kg leptazol; C) reticulospinal IPSP before (1) and 6 min after (2) injection of 10 mg/kg leptazol; D) corticospinal EPSP before (1) and 5 min after (2) injection of 200 mg/kg troxidone; E) reticulospinal EPSP before (1) and 10 min after (2) injection of 10 mg/kg phenytoin.

ability to potentiate the IPSP. IPSP with a long latent period were increased particularly clearly (Fig. 3C). In all 16 observations their amplitude was increased, although sometimes only during the first few minutes after injection of the drug.

Mean values for the amplitude, latent period, and duration of the IPSP at various times after injection of leptazol, together with analogous data for the EPSP, which also showed biphasic changes after administration of this drug, are given in Table 1. It is clear that a stastically significant reciprocal relationship exists between changes in the excitatory and inhibitory potentials: initial depression of the EPSP coincides with potentiation of the IPSP, while subsequent growth of the EPSP is accompanied by a decrease in amplitude of the IPSP.

These facts suggest that during suprasegmental stimulation polysynaptic EPSP may very often consist of the algebraic sum of the EPSP and IPSP, with predominance of the excitatory component. This conclusion agrees with results obtained during artificial polarization by an electric current injected into the cell [2].

Substances with depressant action (troxidone and phenytoin) in most cases lowered the polysynaptic potentials arising during stimulation of the cortex, the red and vestibular nuclei, and the bulbar reticular formation. In the case of troxidone, the decrease in amplitude of the polysynaptic EPSP (fig. 3D) reached 50% on the average. The later part of the response was particularly effectively suppressed. The latent period of the EPSP was slightly increased (from 15 to 20 msec; $P < 0.001$). Polysynaptic IPSP also were depressed by troxidone, as shown by a decrease in their amplitude (from 1.5 to 0.4 mV; $P < 0.002$). Phenytoin lowered the amplitude of the polysynaptic EPSP (Fig. 3E), suppressing responses evoked by cortical and mesencephalic stimulation particularly effectively. However, in some cases the IPSP were actually increased by the action of phenytoin.

The observations described thus reveal a definite qualitative similarity between the sensitivity of the monosynaptic and polysynaptic potentials of afferent [1, 4, 6] and suprasegmental origin to the stimulant leptazol and to substances with depressant action.

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