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Short communication

MODIFICATION OF SPINAL TRANSMISSION BY NIKETHAMIDE

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Nikethamide strongly facilitates spontaneous as well as stimulus-evoked motoneuronal discharge in spinal unanesthetized cats. It does not block presynaptic or postsynaptic inhibition. In experiments on paired dorsal root stimulation (400 msec intervals), it augments the size of the second monosynaptic reflex to an approximately equal level as that of the initially evoked reflex.

Nikethamide Spinal neurons Synaptic transmission

1. INTRODUCTION

Nikethamide (Coramine) is an analeptic agent possessing pronounced convulsant effects on the lower parts of the central nervous system, including the spinal cord (Hahn, 1960). Its effects on synaptic transmission and the mechanism whereby it produces central stimulation are obscure. The following report describes the results of preliminary experiments on the effects of nikethamide on motoneuronal outflow in the spinal cord of the cat.

2. METHODS

Adult cats were anesthetized with ether then spinalized by a section at the atlanto-occipital junction. They were immediately placed under artificial respiration, and ether administration was discontinued. The lumbo-sacral spinal cord was exposed by laminectomy and section of the dura, and covered with warmed mineral oil the temperature of which was kept constant at 37°C. In some experiments, L_5–S_5 dorsal and ventral roots were cut and platinum hook electrodes placed on dorsal and ventral L_7 (DR–VR preparation). In other experiments, dorsal L_6, L_7 and S_1 were left intact on one side, and the appropriate peripheral nerves were isolated and bathed in warm mineral oil. The remaining leg nerves were sectioned. To test membrane excitability, a glass microelectrode filled with 3–4 M NaCl was inserted into a motor nucleus (Wall, 1958). The orthodromic potentials were recorded in the sectioned ventral root, whereas antidromic responses were recorded in the appropriate peripheral nerve. Carotid blood pressure was continuously monitored. Nikethamide was mixed with saline and administered intravenously; it produced an average rise in blood pressure of 13 mm Hg.

3. RESULTS AND DISCUSSION

Nikethamide (50 mg/kg) produced an immediate facilitation of spinal synaptic transmission. The most pronounced effect was observed on the monosynaptic response (MSR) recorded in L_7 ventral root after stimulation of either the corresponding dorsal root or a muscle nerve. The size of this response was increased by about 300% in 5 DR–VR preparations, then gradually returned to near control values in 15–30 min. When the facilitated MSR was superimposed on the control response, no decrease in central latency was observed. Similarly, the afferent

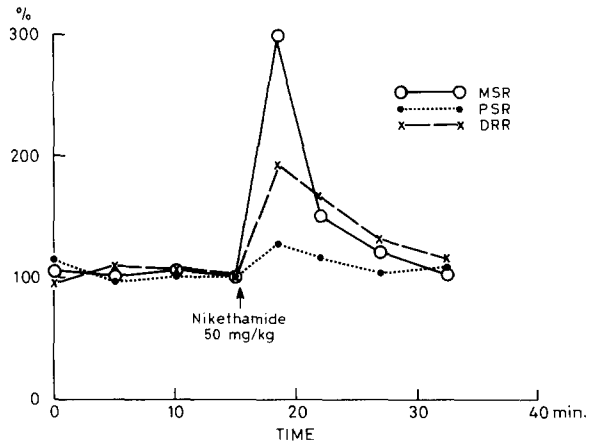

Fig. 1. The effects of nikethamide on spinal transmission. Stimulation (3 times threshold, 12/min) was applied to hamstring flexor nerves and the monosynaptic response (MSR) was recorded in L_7 ventral root whereas the dorsal root reflex (DRR) was recorded in L_6 dorsal root strand. Alternate stimulation (supramaximal) was applied to the sural nerve and the polysynaptic response (PSR) was recorded in ventral L_7. The arrow signals the beginning of nikethamide injection, which lasted 3 min.

input recorded after stimulation of a peripheral nerve showed no change in conduction velocity after nikethamide. Spontaneous activity, measured from a ventral rootlet, was greatly increased. The polysynaptic reflex recorded after stimulation of the sural nerve was mildly facitated. Similarly, the dorsal root reflex, recorded from L_7 dorsal root strand after stimulation of the hamstring nerve, was increased in size by nikethamide. These effects are plotted in fig. 1.

When motoneuronal discharge evoked by gastrocnemius nerve stimulation was inhibited by conditioning trains to the anterior tibial nerve (postsynaptic inhibition) or the hamstring flexor nerves (presynaptic inhibition) at intervals characteristic for these two types of inhibition, no reduction in either type was observed after nikethamide. It therefore appeared that this agent was not acting by mechanisms similar to those of some other known convulsants, such as strychnine (Bradley et al., 1953) or picrotoxin (Eccles et al., 1963).

Direct stimulation of motoneuronal somas with a glass microelectrode did not reveal any change in their membrane potential. This, along with the ability of nikethamide to increase the dorsal root reflex, implicates a presynaptic site of action, as has been proposed for phenols (Banna and Jabbur, 1970). However it differs from phenols in that it does not appear to deplete the transmitter reserves. This was shown by the absence of tachyphylaxis upon repeated administration of nikethamide, and by the equal increase in size of MSRs evoked by double stimulation of the dorsal root at intervals of 400 msec. Since, at such intervals, depletion of transmitter is the predominant factor causing synaptic depression (Curtis and Eccles, 1960), nikethamide may improve transmitter mobilization and release.

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