EFFECT OF DILANTIN ON SPONTANEOUS RHYTHMIC ACTIVITY OF SPINAL CORD INTERNUNCIAL NEURONS AND THEIR RESPONSES TO AFFERENT AND SUPRASEGMENTAL STIMULATION

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The anticonvulsant Dilantin, widely used in neurology, depresses polysynaptic spinal cord reflexes and segmental types of inhibition, and also weakens supraspinal facilitatory and inhibitory reactions [1, 3, 12]. It is suggested that these effects are based on disturbance of the function of the spinal internuncial neurons.

To continue the study of this problem the authors investigated the effect of Dilantin on background activity and evoked responses of single internuncial cells of the spinal cord. Bearing in mind the importance not only of the pyramidal, but also of the extrapyramidal system in the mechanism of the motor manifestations of the fit [4, 7, 8], the action of Dilantin was studied on facilitation and inhibition of internuncial neurons arising during stimulation of the motor cortex and also of the bulbar reticular formation.

EXPERIMENTAL METHOD

Altogether 22 experiments were carried out on anesthetized (30-40 mg/kg Nembutal intraperitoneally) cats. One experiment was carried out on a preparation with low (in the region of the lower thoracic segments) transection of the spinal cord. A few hours after caudal laminectomy, when the action of the anesthetic had worn off, the animal was firmly fixed to a special frame, transferred to artificial respiration, and curarized. Potentials from single internuncial neurons were recorded extracellulary by means of capillary microelectrodes filled with 4 M NaCl solution. The microelectrodes were inserted at the level of the 6th-7th lumbar segments of the spinal cord. After amplification of the potentials with a type UBP-1 ac amplifier, they were recorded on film by a type N-102 loop oscillograph.

The ipsilateral and contralateral dorsal and ventral roots of the 7th lumbar segment, both motor areas of the cortex, and certain bulbar structures were stimulated. The suprasegmental structures were stimulated with bipolar electrodes at a frequency of 150 pulses/sec. The localization of the electrodes in the brain stem (they were introduced through the cerebellum which was left in situ)was determined histologically.

Dilantin was given in increasing doses from 10-30 mg/kg (10-20 mg/kg at 1 time), and in some cases up to 50 mg/kg. The drug was injected intravenously (slowly, at a constant speed of 1-2 mg/kg/min), preventing substantial fluctuations of arterial pressure, which was recorded throughout the experiment in the common carotid artery. Usually the effect of the drug was assessed 5, 10, and 15 min after each injection.

The criterion of the degree of the facilitatory or inhibitory response was the difference between the frequency of the spontaneous rhythmic activity of the neurons before and after stimulation.

EXPERIMENTAL RESULTS

The spontaneous and evoked activity of 60 internuncial neurons located mainly in the dorsal horns of the spinal cord was investigated. The action of Dilantin was studied on 25 cells.

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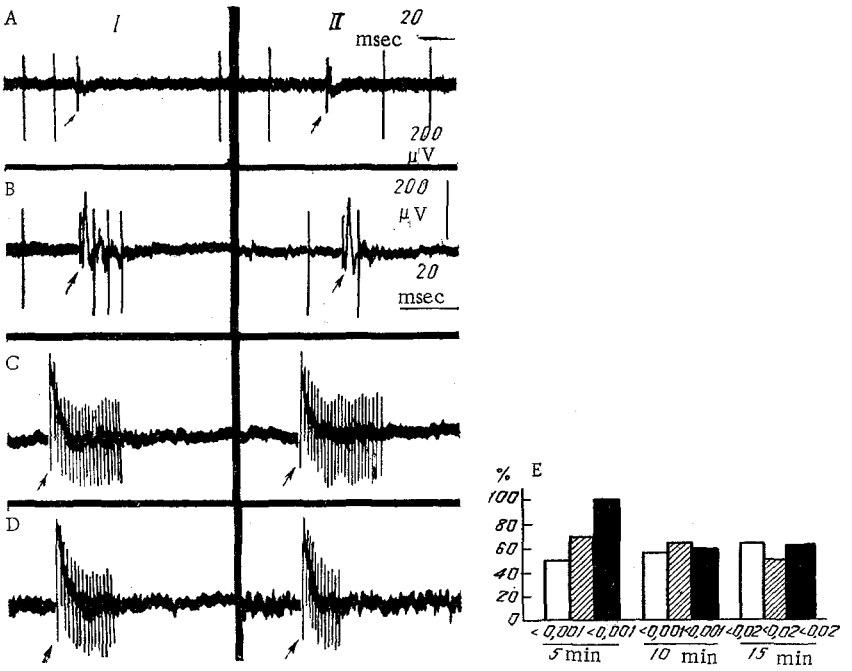

Fig. 1. Disturbance of responses of spinal internuncial neurons to afferent stimulation after injection of Dilantin. I) Normal; II) after injection of Dilantin in a dose of 30 mg/kg; A) inhibition of background rhythmic activity by afferent impulse; B) multiple discharges following activation of another cell; C) responses of Renshaw's cell to stimulation of the ventral root; D) the same cell against the background of stimulation of the contralateral motor cortex (the arrow denotes an artifact of stimulation); E) aggregated dynamics of changes during spontaneous activity (unshaded column), group discharges (shaded column) and inhibitory pauses (black column) under the influence of Dilantin. Columns reflect mean values of corresponding indices (as percent of initial level). Numbers below columns denote criteria of significance of differences (P), bottom row of numbers denotes time (in min) after injection of Dilantin.

Background Activity and Response to Efferent Stimulation. In small doses (10 mg/kg) Dilantin did not alter the character of the spontaneous activity of the internuncial neurons. It produced well marked depression only when the dose of the drug was increased (over 20 mg/kg). The effect was particularly marked in the 5th minute after injection, but by the 15th min of recording it had weakened to some extent, although the difference from the initial level remained statistically significant (Fig. 1A, E). The multiple discharges of the dorsal horn internuncial neurons in response to slightly supramaximal stimulation of the dorsal roots were regularly inhibited by Dilantin (Fig. 1B, E). The number of spikes in the discharge was reduced and the duration of the volley shortened. Similar changes were found when the cells of the spinal animal were investigated. This is in agreement with the reported ability of Dilantin to inhibit repetitive responses of nerve cells selectively [5, 9, 10]. However, in the present experiments, multiple discharges of a Renshaw's cell were not reduced on stimulation of the ventral root, but were actually increased slightly in amplitude (Fig. 1C).

The development of depression of the short-latency responses of the internuncial neurons as a result of rhythmic (40-60 pulses/sec) stimulation of the dorsal root was intensified by Dilantin in agreement with data in the literature indicating that Dilantin accelerates depression of monosynaptic spinal reflexes [3].

Complete suppression of spontaneous activity of certain cells, sometimes following a single or group response of these cells to an afferent stimulus, was preserved after injection of small doses of the drug. With an increase in the dose, these inhibitory pauses were shortened. The effect did not develop at once.

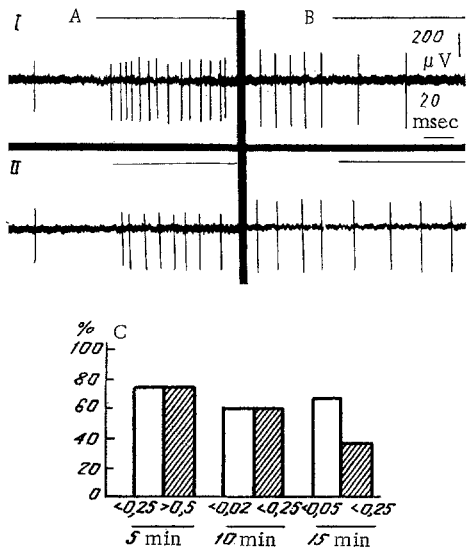

Fig. 2. Effect of Dilantin on facilitation (A) and inhibition (B) of background rhythmic activity during stimulation of ipsilateral motor cortex. I) Normal; II) after administration of Dilantin in dose of 30 mg/kg; C) aggregated dynamics of changes in time of cortical facilitation (unshaded column) and inhibition (shaded column). Horizontal line above represents marker of stimulation of the cortex. Remainder of legend as in Fig. 1E.

Five minutes after injection, in roughly equal numbers of cases, either weakening or strengthening of inhibition was observed. Clearly defined changes took place only after 10-15 min (Fig. 1A, E). The mean duration of inhibition fell from 120 to 70 m/sec. The period of complete inhibition of the background rhythm after short tetanization (at a frequency of 200 pulses/sec) of the dorsal root also was shortened.

It must be concluded from a comparison of the effect of Dilantin on segmental inhibition (using the duration of inhibitory pauses as a criterion) and the effect of facilitation (in the form of multiple discharges) that the former is on the whole more resistant to this drug; it was unchanged after injection of small doses, and was not weakened so quickly after injection of large doses of Dilantin.

The increase in spontaneous rhythmic activity of the spinal neurons during stimulation of the ipsilateral and contralateral motor areas of the cortex was not significantly disturbed by injection of small doses (10 mg/kg) of Dilantin. Essential weakening of the supraspinal reaction developed only 10-15 min after injection of Dilantin in a dose of 20-30 mg/kg (Fig. 2A, C), and even then, in two of the ten cells investigated, facilitation was increased at this time. Meanwhile, under the influence of Dilantin the after-facilitation, in the form of increased frequency of spontaneous activity after cessation of cortical stimulation, was depressed to almost half its initial level. On the whole, this type of tonic response was less resistant to Dilantin than the single responses at the moment of stimulation.

As the results of a separate comparison of the action of Dilantin on ipsilateral and contralateral cortical facilitation of the spontaneous rhythmic activity of the neurons show, in the latter case this effect was weaker. The reason for this difference is most probably a difference in the initial magnitude of the facilitatory response; whereas during stimulation of the contralateral cortex its mean value was 50 pulses/sec, from the ipsilateral motor area it was only 33 pulses/sec.

Dilantin had a less definite influence on cortical inhibition of the background activity of the internuncial cells. Despite the fact that in the aggregate the degree of disturbance of inhibition was identical, and by the 15th min it actually exceeded depression of the facilitatory response by a slight margin, this shift was not statistically significant (Fig. 2B, C). This may have been due to the considerable variability of the results obtained during investigation of individual neurons. Of the 14 cells, strengthening of inhibition was observed in 3 after injection of Dilantin (in a dose of 30 mg/kg), in 4 cells it was unchanged, and only in 7 cells was inhibition weakened. On two occassions an inhibitory effect was converted into facilitatory, and this caused an appreciable change in the magnitude of the overall index. Such conversion has also been described during a study of the action of Dilantin on cortical inhibition of a monosynaptic spinal reflex [12]. At the same time, the anticonvulsant abruptly shortened the duration of poststimulation depression of spontaneous activity, and in one experiment it strengthened the suprasegmental inhibition of evoked discharges of a Renshaw's cell (Fig. 1D).

As the results obtained show, facilitation of the spontaneous activity of the internuncial cells during stimulation of the bulbar reticular formation was weakened after injection of Dilantin in a dose of 20-30 mg/kg (Fig. 3A, C). This effect was seen in most cells, but in 3 of the 12 cells, on the contrary, the facilitation was increased. Histological verification of the position of the stimulating electrodes demonstrates that usually the reticular nuclei of the caudal third of the brain stem (the parvo- and magnocellular, ventral, and caudal nuclei of the pons), and the nuclei of the vagus and trigeminal nerves were stimulated. The main mass of these structures has no direct connections with the lumbar segments of the spinal cord [2]. Impulses from them travel to the spinal cells along complex polyneuronal pathways, and this is evidently responsible for their sensitivity to Dilantin.

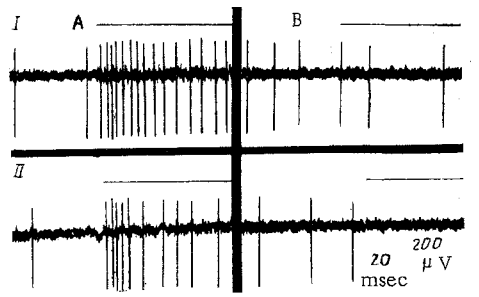

Fig. 3. Changes in bulbar facilitation (A) and inhibition (B) of activity of spinal internuncial neurons by Dilantin. I) Normal; II) after injection of Dilantin, C) aggregated dynamics of changes in time of facilitatory reaction during stimulation of the bulbar reticular formation. Localization of the electrodes is shown in the diagram. Horizontal line represents marker of stimulation of the brain stem. Remainder of legend as in Fig. 1E.

The effect of the anticonvulsant on bulbar inhibition of the internuncial neurons was examined in detail in only 4 cells: in one case it was unchanged, in 2 it was completely suppressed, and in 1 it was strengthened. Deepening of inhibition was observed during stimulation of the reticular gigantocellular nucleus (Fig. 3B), the inhibitory responses of which are especially resistant to Dilantin [1].

On the whole the facilitatory responses were more sensitive than the inhibitory.

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