EFFECT OF ANALGESICS AND ANESTHETICS ON DORSAL ROOT POTENTIALS EVOKED BY AFFERENT NERVE STIMULATION

Yu. D. Ignatov

UDC 615.212.7.015

Experiments on unanesthetized cats showed that morphine, trimeperidine, and sodium hydroxybutyrate have a biphasic action on dorsal root potentials (DRPs): they were increased by small doses (1-3, 2-4, and 25-50 mg/kg respectively) and inhibited by large doses (6-10, 8-12, and 400-600 mg/kg). The facilitatory effect in the first phase of action was stronger in relation to DRPs of a cutaneous nerve, more especially with morphine. Phentanyl and pentobarbital caused no initial increase in DRP. The substances tested produced different changes in the facilitatory effect of spinalization on DRPs. The reasons for the change in DRPs under the influence of these drugs are discussed and the possible mechanisms of their analgesic action at the spinal level are considered.

There have been few investigations of the effect of analgesics and anesthetics on presynaptic inhibition [5-7, 9, 14]. Most workers assess the effect of the substances they have tested by changes in the dorsal root potentials (DRPs) evoked by stimulation of the neighboring dorsal root. It is postulated [8, 16] that control over the afferent input of cutaneous and muscular fibers is effected by different neuronal mechanisms depending on the different functions concerned.

It was therefore decided to make a comparative study of the action of analgesics and anesthetics on dorsal root potentials evoked by stimulation of cutaneous and muscular nerves.

EXPERIMENTAL METHOD

Experiments were carried out on unanesthetized curarized cats. The animal was anesthetized deeply with ether for the preoperative preparations. DRPs evoked by a single stimulation (3-15 V; 0.3-0.5 msec) of cutaneous (sural and superficial peroneal) and muscular (gastrocnemius) nerves were recorded from filaments of dorsal roots L_7-S_1 by platinum electrodes. Changes in the excitability of the primary afferent fibers [15] were determined. Intraspinal stimulation of the cutaneous and muscular nerve afferents was carried out through metal electrodes with a tip 20-30 μ in diameter. Potentials (UBP-02 amplifier, time constant about 0.5 msec) were recorded from the screen of a cathode-ray oscilloscope. In individual experiments spinalization was carried out at the levels T_{10}-T_{12}-L_1.

The drugs were injected intravenously in the following doses: morphine from 1 to 8-10 mg/kg, trimeperidine from 2 to 10-12 mg/kg, phentanyl from 0.01 to 0.2 mg/kg, pentobarbital from 5 to 40-50 mg/kg, chloralose from 20 to 600 mg/kg, and sodium hydroxybutyrate from 20 to 120 mg/kg.

EXPERIMENTAL RESULTS

The original DRPs in these experiments corresponded to the established standards and differed only in their shorter duration (120-150 msec); this showed that the functional state of the dorsal roots was good [10], probably on account of the absence of anesthesia.

Department of Pharmacology, I. P. Pavlov First Leningrad Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 76, No. 9, pp. 52-56, September, 1973. Original article submitted October 30, 1972.

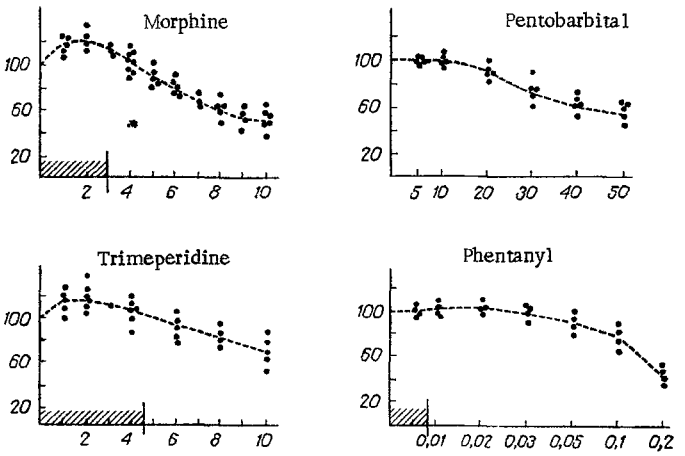

Fig. 1. Effect of analgesics and pentobarbital on dorsal root potentials (DRPs) evoked by stimulation of a cutaneous nerve. Abscissa, dose (in mg/kg); ordinate, amplitude of DRP (in %). Points represent results of individual experiments, broken line gives mean values.

The pooled data for changes in DRPs evoked by stimulation of a cutaneous nerve following administration of the drugs, together with individual records, are shown in Figs. 1 and 2. Morphine and trimeperidine had a biphasic action on the DRPs, increasing them in small analgesic doses (1-3 and 2-4 mg/kg respectively) and inhibiting them in larger doses (6-10 and 8-12 mg/kg). These analgesics were found to have a biphasic action when given within the same range of doses in tests of the excitability of intraspinal afferents. Morphine in small doses led to a greater increase in DRPs evoked by stimulation of the homonymous nerves than trimeperidine (Fig. 1). In the first phase of action of these substances, the duration of the DRPs was increased as well as their amplitude (Figs. 2 and 3).

Under the influence of morphine in a dose of 1-2 mg/kg an additional component of the DRP appeared in response to stimulation of the cutaneous nerve after a latent period of 30-45 msec (Fig. 2A). During this same time interval an additional wave was found in the curve of the change in excitability of the terminals. The additional wave in the DRP of the muscular nerve during the action of morphine was inconstant and it arose more often in response to stimulation of above-threshold strength. This ability of morphine in doses of 1-2 mg/kg to evoke a second component of the DRP is in agreement with observations made by other workers [14]. The second component of the DRP generated under the influence of various factors [4, 12, 14] is considered to be due to the removal of suprasegmental inhibition.

To elucidate the role of descending influences in the manifestation of this facilitatory effect of morphine and trimeperidine on the DRP, the degree of increase in the DRP before and after spinalization was compared. Whereas under normal conditions spinalization was accompanied by an increase in amplitude of the DRPs (in agreement with data in the literature [12]) its effect was very slight when superposed on the action of the analgesics. Moreover, the additional component of the DRP produced under the influence of morphine was completely abolished by spinalization. It can therefore be concluded that the facilitatory action of these drugs in small doses on the DRP is connected with the removal of suprasegmental inhibition. The suppression of descending inhibitory influences by analgesics has been demonstrated previously [1,2]. On the other hand, the increase in DRPs under the influence of morphine and trimeperidine could be the result of their segmental action and caused either by a decrease in the strength of hyperpolarization effects, as shown by the prolongation of the DRP, or by an increase in activity of the neurons responsible for the generation of primary afferent depolarization. It has been shown previously [3] that morphine, in doses of 1-3 mg/kg, increases the activity of the cells of the substantia gelatinosa.

Phentanyl in doses of between 0.01 and 0.1 mg/kg caused no significant change in DRPs of cutaneous or muscular nerves. Similar results have been obtained by other workers [11]. In some cases, however, an increase in the duration of the DRP of the cutaneous nerve was found (Fig. 2B). Under the influence of large doses of phentanyl (0.1-0.2 mg/kg) the DRP was sharply inhibited.

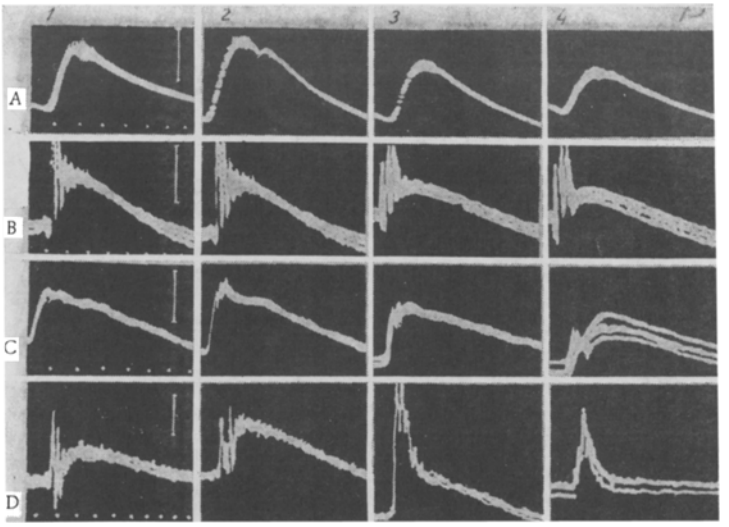

Fig. 2. Effect of morphine (A), phentanyl (B), trimeperidine (C) and sodium hydroxybutyrate (D) on DRP of cutaneous nerve: 1) normal; 2,3,4) after administration of: A) morphine in doses of 2, 4, and 8 mg/kg respectively, B) phentanyl in doses of 0.01, 0.05, and 0.1 mg/kg, C) trimeperidine in doses of 3, 6, and 10 mg/kg, and D) sodium hydroxybutyrate in doses of 25, 200, and 600 mg/kg respectively. Calibration: time 20 msec, amplitude 250 μV. All records obtained by superposition of 4 to 6 sweeps of the beam.

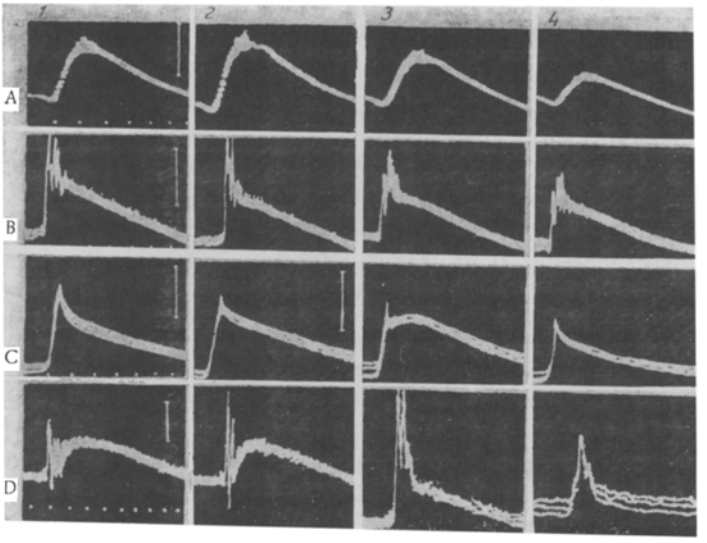

Fig. 3. Effect of morphine (A), phentanyl (B), trimeperidine (C), and sodium hydroxybutyrate (D) on DRP of muscular nerve. Legend as in Fig. 2.

Pentobarbital within a wide range of doses (5-20 mg/kg) had no significant effect on the amplitude of the DRP although an increase in duration of the potentials was constantly found. By contrast with phentanyl, pentobarbital reduced the facilitatory effect of spinalization on the DRP. This property of pentobarbital was exhibited most clearly in doses of 10-15 mg/kg. Pentobarbital in doses greater than 20 mg/kg causes a progressive decrease in DRP.

According to data in the literature sodium hydroxybutyrate in doses of 25-75 mg/kg does not affect [9] or inhibits [7] DRPS. In the present experiments these doses of this compound led to a small (by 15-20%)

increase in the amplitude of the DRPs of the cutaneous nerve (Fig. 2D) but had no significant effect on DRPs of the muscular nerve (Fig. 3D). Injection of sodium hydroxybutyrate in large doses was followed by a decrease in DRPs of the cutaneous and muscular nerves. Under the influence of the compound in doses of 100-300 mg/kg an additional component with a latent period of 35-50 msec was recorded. This late component was virtually not observed in DRPs evoked by stimulation of the muscular nerve. The late wave of the DRP disappeared completely after spinalization, although this, in turn, had only very little effect on the increase in the cutaneous DRP produced by the action of sodium hydroxybutyrate in doses of 25-50 mg/kg. Under the influence of sodium hydroxybutyrate in doses larger than 50 mg/kg the decrease in DRP was accompanied by a simultaneous increase in the dorsal root reflex, in agreement with observations made by other investigators [6, 7].

Chloralose in doses of 20-60 mg/kg had no significant effect on the DRP. Large doses of the anesthetic (60-120 mg/kg) led to inhibition of the DRP and a simultaneous splitting of the potential into two components. The facilitatory effect of spinalization on the DRP was unaffected by chloralose.

These results show that the drugs investigated cause different changes in DRPs evoked by stimulation of cutaneous and muscular nerves, a result attributable to the different neuronal organization of the sources of DRP generation. The increase in DRP under the influence of small "analgesic" doses of morphine and trimeperidine, indicating "closure" of the segmental afferent input, lies at the basis of the elevation of the pain threshold which is one component of the pharmacological action of these analgesics. The strengthening of primary afferent depolarization under the influence of these drugs may be caused either by the abolition of the hyperpolarizing effects of the thin "nociceptive" fibers [13] or by changes in the descending influences directed toward the afferent input system.

These observations showing differences in the degree of increase in the DRP under the influence of morphine, trimeperidine, pentobarbital, sodium hydroxybutyrate, and chloralose are in good agreement with the well-documented unequal analgesic activity of these drugs. Phentanyl, which does not change the DRP, evidently has no segmental component in the mechanism of its pain-relieving action, and its analgesic effect is attributable to its influence at the superspinal level.

LITERATURE CITED

1. É. B. Arushanyan, in: Investigations into the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian], Leningrad (1961), p. 108.
2. A. V. Val'dman, in: New Data on the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian], Leningrad (1958), p. 64.
3. Yu. D. Ignatov, Byull. Éksperim. Biol. i Med., No. 11, 71 (1970).
4. Yu. D. Ignatov, Fiziol. Zh. SSSR, 57, No. 11, 1607 (1971).
5. N. A. Kruglov, Farmakol. i Toksikol., No. 4, 395 (1968).
6. N. A. Kruglov and R. I. Kvasnoi, Farmakol. i Toksikol., No. 3, 263 (1968).
7. N. A. Kruglov and R. I. Kvasnoi, in: Sodium Hydroxybutyrate [in Russian], Moscow (1968), p. 48.
8. J. C. Eccles, in: The Physiology of Synapses, Academic Press (1964).
9. J. M. Besson, J. P. Rivot, M. Abdelmoummenne, et al., Neuropharmacology, 10, 141 (1971).
10. G. D. Dawson, E. G. Merill, P. D. Wall, et al., Science, 167, 1385 (1970).
11. N. Iwata and Y. Sakai, Jap. J. Pharmacol., 21, 427 (1964).
12. A. Lundberg, Progr. Brain Res., 12, 197 (1964).
13. R. Melzack and P. D. Wall, Science, 150, 971 (1965).
14. A. Tang, Exp. Neurol., 25, 393 (1969).
15. P. D. Wall, J. Physiol., 12, 1 (1958).
16. P. D. Wall, Progr. Brain Res., 11, 92 (1964).