PHARMACOLOGY OF AZIDOMORPHINE

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UDC 615.212.7:547.943

Acute experiments on rabbits, cats, and rats showed that new synthetic morphine-like analgesic azidomorphine surpasses morphine in its ability to inhibit synaptic transmission in thalamic structures, the cerebral cortex, and the spinal cord during nociceptive stimulation, and also is 20-100 times stronger in its analgesic activity.

KEY WORDS: azidomorphine; morphine; thalamus; cortex; spinal cord.

With the appearance of the new narcotic analgesic azidomorphine, 40-50 times stronger than morphine in its analgesic activity [5-10], it was interesting to compare the effect of the two drugs on synaptic transmission of excitation in different parts of the CNS. For this purpose, two techniques were used: the method of impulse summation in the CNS and the method of extracellular recording of spontaneous and evoked unit activity in the somatosensory cortex and spinal cord. As was shown previously [3], summation of impulses in the CNS is affected by morphine in relatively small doses, namely 0.5 mg/kg for rabbits, or 1/600 of the lethal dose. Changes in impulse summation in the CNS under the influence of morphine, as a special analysis has shown, are primarily associated with its action on thalamic formations [4]. The effect of morphine on synaptic transmission in the cortex and spinal cord has been shown by several workers [1, 2, 13].

EXPERIMENTAL METHOD

Impulse summation in the CNS was investigated in experiments on normal rabbits during nociceptive (electric shock) stimulation of the hind limb at a frequency of 2 stimuli/sec, the duration of each stimulus being 10 msec. The number of stimuli of a particular amplitude was recorded at which flexion of the stimulated limb developed (unconditioned reflex).

The sensitivity of synapses of the somatosensory cortex and of the spinal cord to morphine and azidomorphine was determined by the method of recording unit activity. Experiments were carried out on cats weighing 2-3 kg and on rats weighing 250-300 g. Tracheotomy, and catheterization of the veins and arteries were carried out under ether anesthesia. The animal was then fixed to a special frame, immobilized with anatruxonium (0.1-0.2 mg/kg), and artificially ventilated. Unit activity was recorded by steel microelectrodes with a tip 1-3 μ in diameter. Unit activity was recorded by means of a PP-15 scaler with printing attachment, continuously throughout the experiment. Intraarteriole injection of bradykinin (10 μg) was used as the method of specific nociceptive stimulation [11]. Morphine, azidomorphine, and nalorphine were injected intravenously. Control experiments showed that, in the doses used, these drugs caused practically no change in the blood pressure.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that azidomorphine, like morphine, has a depriming effect on impulse summation in the CNS (Fig. 1), but in much smaller doses than morphine. For instance, in rabbits morphine weakened impulse summation in the CNS in a dose of 0.5-1 mg/kg, whereas azidomorphine did so in a dose of 0.005-0.01 mg/kg. According to this parameter, therefore, azidomorphine is 100 times stronger than morphine. The phenomenon of impulse summation in the CNS reflects the analgesic activity of narcotic analgesics, and in this case, as was stated above, its action is effected mainly at the thalamic level [4].

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0007-4888/78/8506-0749$07.50

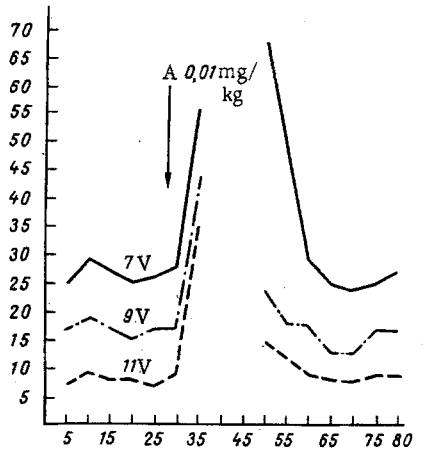

Fig. 1

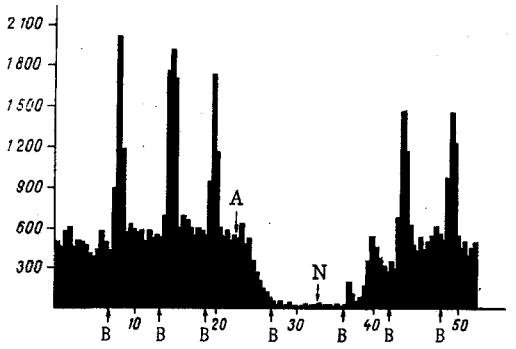

Fig. 2

Fig. 1. Effect of azidomorphine on impulse summation in the CNS. Abscissa, time (in min); ordinate, number of stimuli; figures on curves show amplitude of stimuli (in V). A) Intravenous injection of azidomorphine in a dose of 0.01 mg/kg.

Fig. 2. Effect of azidomorphine and nalorphine on spontaneous and bradykinin-evoked unit activity in the sensomotor cortex. Columns show number of spikes in every 30 sec. B) Intra-arterial injection of bradykinin (10 μg); A) intravenous injection of azidomorphine (0.3 mg/kg); N) intravenous injection of nalorphine (3 mg/kg). Remainder of legend as in Fig. 1.

TABLE 1. Comparative Activity of Morphine and Azidomorphine

Drug	Isolated organs containing opiate receptors			Hot plate test		Spasm test	Tail retraction test	Algolytic test	Chronic unrelieved pain (effective dose in man, mg)
	guinea pig intestine	mouse vas deferens	cat nictitating membrane	ED_{50}, mg/kg (subcutaneously)					
	D_{50}, nmoles			mice	rats	mice	rats	rats	
Morphine	1	1	1	1	1	1	1	1	1
Azidomorphine	28	7	21	60	128	20	150	75	40

The study of the effect of morphine on spontaneous and bradykinin-evoked unit activity in the sensomotor cortex gave the following results. Morphine in a dose of 1.5 mg/kg reduced spontaneous unit activity compared with its initial level by 80-90%. In this dose morphine also completely abolished the increase in unit activity evoked by bradykinin. Against this background nalorphine, in a dose of 1.5-2 mg/kg, increased the spontaneous discharge frequency to its initial level and restored the response of the neurons to bradykinin. With an increase in the dose to 3 mg/kg, morphine almost completely suppressed spontaneous unit activity. The response of neurons to bradykinin was restored and the spontaneous discharge frequency increased 5-6 min after injection of nalorphine (2-3 mg/kg), but this recovery did not reach the original level. The inhibitory action of morphine was clearly manifested in experiments on both cats and rats. It is important to note that after intravenous injection of morphine in a dose of 1.5-3 mg/kg analgesia is observed in rats [1].

In most experiments azidomorphine, like morphine, depressed spontaneous and bradykinin-evoked unit activity in the sensomotor cortex. In an analgesic dose for rats of 0.02-0.03 mg/kg [5], for instance, in some experiments azidomorphine reduced the spontaneous discharge frequency by almost half and completely abolished the response to bradykinin. In a dose of 0.3 mg/kg azidomorphine almost totally suppressed spontaneous and bradykinin-evoked activity. Nalorphine, in a dose of 1.5-3 mg/kg, abolished the depriming effect of

azidomorphine (Fig. 2). In some experiments azidomorphine, in the same doses (from 0.03 to 0.3 mg/kg) had no marked inhibitory action on spontaneous and evoked unit activity.

The direction of the action of morphine and azidomorphine at the spinal level was assessed by studying the ability of these drugs to inhibit bradykinin-evoked unit activity of interneurons in the posterior horns of the spinal cord. The role of these neurons in the response to nociceptive stimulation was established previously [12, 14].

These experiments showed that morphine in a dose of 1 mg/kg inhibits bradykinin-evoked activation of interneurons of the posterior horns. With an increase in the dose of the drug to 2-3 mg/kg, activation was completely suppressed. Azidomorphine began to inhibit evoked activity in a dose of 0.1-0.05 mg/kg and completely suppressed the response of the neurons to bradykinin in a dose of 0.2-0.3 mg/kg. The depriming action of morphine and azidomorphine was abolished by nalorphine. Morphine and azidomorphine thus inhibit the response of the neurons, but the depriming action of azidomorphine is 10 to 20 times stronger than that of morphine.

These experiments thus showed that azidomorphine, like morphine, depressed synaptic transmission during nociceptive stimulation in the thalamus, cerebral cortex, and spinal cord. However, the depriming activity of azidomorphine is manifested in much smaller doses than the analogous effect of morphine. For instance, azidomorphine inhibits synaptic transmission in the cerebral cortex, thalamus, and spinal cord in doses 75, 100, and 20 times smaller respectively than morphine. It is important to note that the doses of morphine and azidomorphine which inhibit synaptic transmission at the cortical, thalamic, and spinal levels are close to or the same as the doses of the drugs causing analgesia in rats.

The results showed that the unequal sensitivity of the cerebral cortex, thalamus, and spinal cord to morphine and azidomorphine correlates with the doses of these drugs in which they cause analgesia in animals and man, and also contraction of isolated organs containing opiate receptors (Table 1).

Morphine and azidomorphine thus act in a similar way by inhibiting the transmission of impulses during nociceptive stimulation at different levels in the CNS. The absence of any differences, in principle, between the action of azidomorphine and morphine is also confirmed by the fact that nalorphine, an antagonist of the narcotic analgesics, abolishes the depriming effect of both drugs.

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