SELECTIVITY OF ANALGESIC EFFECTS OF ANGIOTENSIN AND BOMBESIN AGAINST DENTAL AND CUTANEOUS NOCICEPTIVE STIMULI

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During the action of nociceptive stimuli of varied nature the secretion of different peptides and, in particular, of somatostatin and substance P, has been demonstrated at the level of relay neurons of the spinal cord [7], and certain peptides, notably neurotensin and calcitonin, have been shown to have a selective analgesic action, depending either on the nature of the nociceptive stimulation [3] or on its localization [4]. Angiotensin II and bombesin, which are endogenous nonopioid peptides [5, 8], are widely represented in structures of the CNS and, in particular, in the region of the posterior horn of the spinal cord, the brain stem, thalamus, and so on, and also in the descending supraspinal tracts running to the posterior horn [6]. This indicates their possible participation in the physiological mechanisms of modification of nociceptive sensation, and differences in their localization both with each other and with the opioid peptides have given rise to the suggestion that they may have different influences on nociception depending on the genesis or location of the nociceptive stimulation.

In the investigation described below two types of nociceptive stimulation were studied: electrocutaneous and electrodental, for differences in their perception are well known from clinical practice. Since the most adequate parameter of nociception in animals is a change in evoked potentials (EP) of brain structures [2], and because of the considerations expressed above, the aim of the present investigation was to study the action of angiotensin II and bombesin on changes in somatosensory cortical EP of rabbits in response to electrodental and electrodermal nociceptive stimulation.

EXPERIMENTAL METHOD

Experiments were carried out on 40 conscious and loosely restrained male chinchilla rabbits weighing 2.5-3 kg, previously scalped under procaine anesthesia. EP were recorded from the surface of the cranial bones in the region of the somatosensory cortex in response to electrocutaneous stimulation of the contralateral hind limb (ECS), causing limb withdrawal, and electrodental stimulation (EDS), causing a licking reflex, which could be produced with the aid of electrodes inserted into the pulp of the upper incisors (single square pulses, 0.5 msec, 4-20 mA). One animal was used in each experiment. By means of a cannula fixed beforehand to the skull, a solution of bombesin (from "Serva") in a dose of 20 μg/kg (14 experiments), and a solution of angiotensin II (A II) in a dose of 50 mg/kg ("Sigma") (20 experiments), were injected in a volume of 10 μl into the third ventricle; naloxone ("Endo") was injected in a dose of 0.15 mg/kg in a volume of 1 ml intravenoulsy (six experiments). EP were analyzed on an NTA-1024 amplitude-phase analyzer in 10 realizations. The amplitude of the component (AC) P_{20-40} of EP, the one most associated with nociception [2], was determined in the animals in the initial state and at 10-min intervals after injection of the peptides. For each experiment the average background values of AC of P_{20-40} of EP were determined, and taking this value as 100%, deviations at different times were calculated. The significance of differences between the results was estimated by nonparametric statistical tests and by Student's test.

EXPERIMENTAL RESULTS

In response to ECS a primary response (PR) with a latent period (LP) of 10-12 msec and an amplitude of 15-50 μV, and also a marked secondary negative–positive component with LP of

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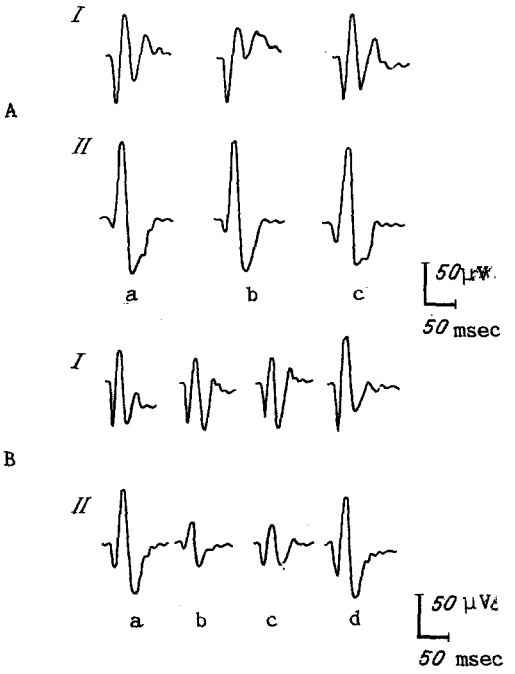

Fig. 1. Changes in EP (n = 10) of somatosensory cortex of rabbit in response to EDS (I) and to ECS (II) before (a), and 25 (b), and 100 min (c) after injection of A II (A) and 20 min (b), 80 min (c), and 120 min (d) after injection of bombesin (B).

20-40 msec and an amplitude of 100-160 μV were recorded in the somatosensory cortex (Fig. 1, A, II). In response to EDS the EP had a PR with LP of 8-12 msec and an amplitude of 50-70 μV and a well marked secondary negative–positive deviation with LP of 20-40 msec and an amplitude of 80-100 μV (Fig. 1, A, I). EP were recorded at the point in which the greatest change in AC of P_{20-40} of EP was found in response to a change in strength of the nociceptive electrical stimulus. The initial values of EP were recorded from 40-60 min.

Bombesin caused no significant change in the value of AC $P_{20\ 40}$ of EP in response to EDS (Fig. 1, B, I; Fig. 2, B). At the same time, bombesin caused a significant (up to 40%) decrease in P_{20-40} of EP in response to ECS from the 5th to the 70th min, after injection (Fig. 1, B, II; Fig. 2, B). Values of the initial amplitude of the EP component were usually recorded by the 100th min.

Injection of A II led to a fall in AC P_{20-40} of EP in response to EDS on average by 45-50% during the 40 min after injection (Fig. 1A, 1; Fig. 2, A). Values of the amplitude of this EP component in response to EDS returned to their initial levels after 50 min. Meanwhile injection of A II caused no significant change in AC P_{20-40} of EP in response to ECS (Fig. 1, A, II; Fig. 2, A).

Systemic administration of naloxone 20-25 min after injection of A II had virtually no effect on the time course of changes in AC P_{20-40} of the somatosensory cortical EP in response to EDS. The duration and amplitude of the effect of A II remained the same as before.

Thus A II led to a naloxone-independent reduction of AC P_{20-40} of the somatosensory cortical EP in response to EDS but did not change it in response to ECS. Bombesin had the opposite effect. Since this component of the somatosensory cortical EP in the rabbit correlates with the degree of pain perception [2], it can be tentatively suggested that A II has a selective analgesic effect against dental pain but does not affect cutaneous pain, whereas bombesin has a selective analgesic effect on the latter and does not affect the former. Characteristically A II likewise did not act on pain sensitivity in response to thermal and mechanical nociceptive cutaneous stimuli [5], whereas bombesin, on the contrary, gave a naloxone-independent analgesic effect on their action [8]. Taken in conjunction with our own data on the effect of naloxone, this observation points to the absence of involvement of the endogeneous opioid system in modulation of the nociceptive stimulus, a characteristic feature of which is

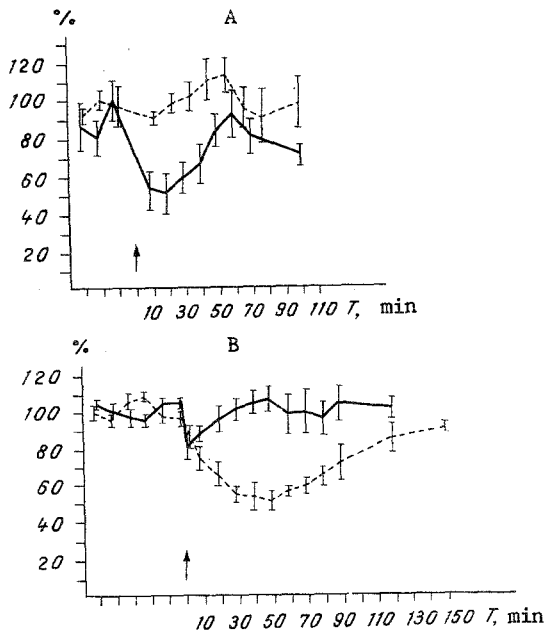

Fig. 2. Time course of changes in amplitude of P_{20-40} of EP (n = 10) of rabbit somatosensory cortex in percent of average background values before and after injection of A II (A) and bombesin (B) in response to EDS (continuous line) and to ECS (broken line). Abscissa, time (in min); ordinate, amplitude (in %). Arrow indicates time of injection of substance.

nonspecificity of the analgesic effects and independence of the genesis and location of the nociceptive stimulus [1].

The selectivity of the analgesic effects of A II and bombesin thus revealed may be due to definite differences in the peptide mechanisms of dental and cutaneous pain and, in turn, this is probably connected with certain structural differences in the conduction of nociceptive impulses from foci in different locations. For instance, trigeminal structures of the brain play a major role as relay nuclei for impulsation from the dental pulp, which contains A II receptors [9], whereas the presence of bombesin, but not of A II, has been described in the region of neurons of the posterior horn of the spinal cord, receiving impulsation from the skin of the limbs [6].

Selectivity of the antinociceptive action of A II and bombesin in the present investigation, and also of neurotensin, cholecystokinin, and calcitonin in experiments by other workers [3, 4] suggests that besides opioid endogenous nonspecific mechanisms of antinociception, there also exist in the body specific peptide mechanisms, linked to a greater or lesser degree with the genesis of pain excitation. This indicates the possibility of a basically new approach to the search for and use of effective pain-relieving agents and of new methods of treatment of pain syndromes related to their genesis.

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