ROLE OF OPIOIDERGIC AND ADRENERGIC MECHANISMS IN THE ANALGESIC EFFECT OF CLONIDINE

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Clonidine, which has a central adrenopositive action, has a broad spectrum of pharmacological effects, including analgesia, manifested by inhibition not only of emotional-behavioral, but also of hemodynamic nociceptive reactions [2, 11, 14]. Despite intensive study of the neurochemical bases of the hypotensive and various psychotropic effects of clonidine [1, 9, 10], the mediator and receptor mechanisms of clonidine-induced analgesia have definitely been inadequately studied, and available data on the role of opioidergic and adrenergic processes in the analgesic action of the drug are contradictory [7, 11, 12].

The present investigation was devoted to a study of these problems.

EXPERIMENTAL METHOD

Experiments were carried out on 64 conscious rats. The perceptive and emotional components of nociceptive reactions were assessed by measuring changes in the latent period of the tail flick and the threshold of vocalization in response to electrical stimulation of the base of the tail [4]. A catheter was introduced into the aorta to record the blood pressure (BP) by the V16-5MA system on a K-21 oscilloscope.

The following substances were injected intraperitoneally in the doses stated (mg/kg): clonidine (from Boehringer Ingelheim, West Germany), 0.1-1 mg/kg, naloxone (Narcan, from Endo Laboratories, USA) 1 mg/kg, reserpine (Rausedil, from Gedeon Richter, Hungary) 5 mg/kg, nisoxetine (from Eli Lilly, USA) 10 mg/kg, prazosin (Praziol, from Orion, Finland) 1 mg/kg, yohimbine (from Regis, USA) 0.5 mg/kg. In a separate series of experiments clondine (2.5-5 μg) and morphine (10-20 μg) were injected into the subdural space of the spinal cord at the level of the middle lumbar segments [13].

The numerical results were subjected to statistical analysis by the usual methods.

EXPERIMENTAL RESULTS

Clonidine in doses of 0.25 to 1 mg/kg inhibited the emotional and perceptive components of the nociceptive response and, at the same time, raised BP (Fig. 1), probably due to the marked peripheral vasoconstrictor action of the drug in doses of 0.1 mg/kg and higher, masking its central hypotensive effect [16]. The results are evidence that the analgesic effect of clonidine in doses of 0.25 to 1 mg/kg is unconnected with parallel shifts developing in the background BP levels, and they do not confirm the existing view [15] that inhibition of the emotional-painful response by the action of clonidine is due to weakening of the animals' reactivity to aversive stimuli through depression of sympathetic tone and lowering of BP.

Besdies inhibiting the emotional-behavioral manifestations, clonidine also inhibited pressor responses of BP to stimulation of the base of the rats' tail, evoking vocalization (Fig. 1: 2). Reduction of the hemodynamic responses was not dose-dependent in character and it developed over the range of both analgesic and subanalgesic (0.1 mg/kg) doses. Inhibition of the nociceptive responses of BP distinguishes clonidine from morphine-like drugs which, administered systematically in analgesic doses, do not significantly inhibit the hemodynamic components of the nociceptive response in animals and man [3, 5]. Very probably this difference is to some

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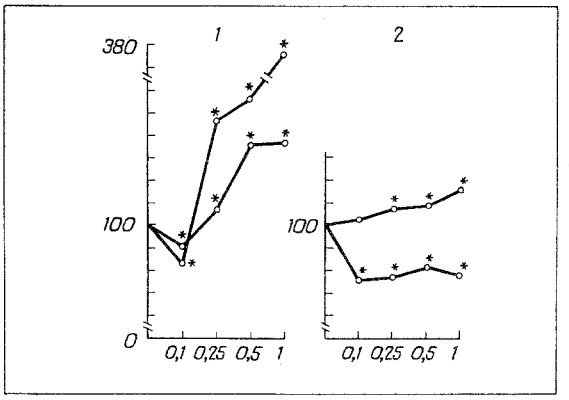

Fig. 1. Effect of clonidine on emotional behavioral and hemodynamic nociceptive responses of rats. Abscissa: dose of clonidine (in mg/kg); ordinate, changes in parameters (in %): 1) latent period of tail flick in response to temperature stimulation (empty circles) and vocalization thresholds during electrical stimulation (filled circles); 2) BP (empty circles) and pressor responses to electrical stimulation of base of tail (filled circles) † *P < 0.05.

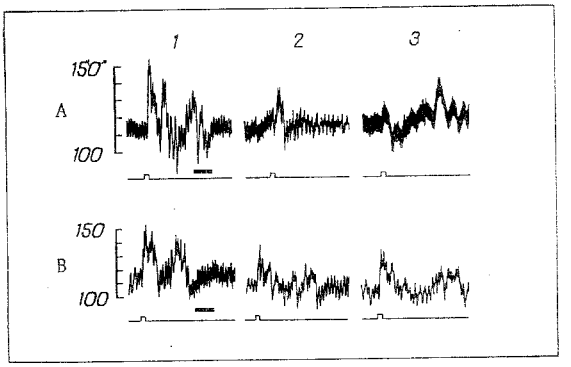

Fig. 2. Changes in nociceptive responses of BP to injection of clonidine (A) and morphine (B) into subdural space of rat spinal cord. 1) Control; 2, 3) 5 and 15 min respectively after injection of clonidine (2.5 μg) or morphine (20 μg). From top to bottom: BP, marker of stimulation of base of tail. Time marker 5 sec.

extent due to differences in the effects of clonidine and narcotic analgesics on the mechanisms of regulation of the circulation, especially at the segmental level. The results (Fig. 2) show that clonidine and morphine, injected subdurally in doses weakening the behavioral manifestation of pain equally, clonidine depresses hemodynamic nociceptive responses much more strongly than morphine.

We know that clonidine can not only act on adrenergic mediation processes, but can also modify the affinity of opioids for different types of opiate receptors [8]. From the standpoint of this receptor interaction, we can explain the abolition of the withdrawal syndrome in opiate-dependent subjects and certain other effects of clonidine [8, 11]. However, in our view, opioidergic mechanisms have no essential role in the formation of the analgesic action of clonidine. This conclusion is based on experimental data showing that naloxone did not weaken the effect of clonidine on emotional-behavioral and hemodynamic components of nociceptive reactions (Fig. 3). Further analysis, using adrenolytic drugs, suggested that the analgesic action of clonidine was due to activation of brain andrenergic processes.

†Figure as in the Russian text. It is not obvious which set of circles should be filled in – Editor.

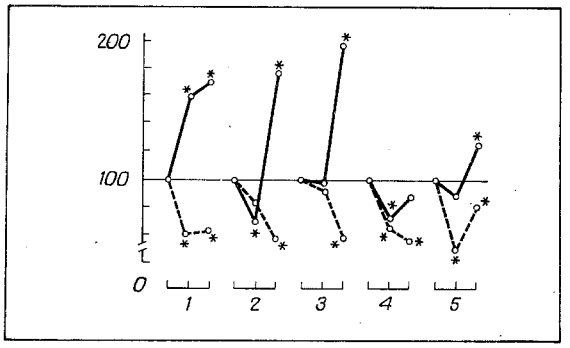

Fig. 3. Effect of naloxone and adrenolytic drugs on analgesic effect of clonidine (0.5 mg/kg). 1) Clonidine and naloxone (1 mg/kg); 2) reserpine (5 mg/kg) and clonidine; 3) nisoxetine (10 mg/kg) and clonidine; 4) prazosin (1 mg/kg) and clonidine; 5) yohimbine (0.5 mg/kg) and clonidine; ordinate: changes (in %) in latent period of tail flick (continuous lines) and pressor responses of BP (broken lines).

In reserpinized animals (5 mg/kg, 24 h before the experiment), for instance, clonidine analgesia proved stronger than inhibition of emotional-behavioral nociceptive responses in the control group of rats (Fig. 3). Reserpinization exhausts presynaptic reserves of catacholamines, and thereby creates a situation in the synapses in which the effect of clonidine can be realized mainly through postsynaptic adrenoreceptors. The results thus suggested that the analgesic action of clonidine is due to activation of central α_1-adrenoreceptors. The validity of this suggestion is confirmed by the results of experiments with nisoxetine, an inhibitor of catecholamine reuptake [17], and with prazeosin, a highly selective α_1-adrenolytic (Fig. 3). Nisoxetine considerably potentiated analgesia due to clondine. After preliminary administration of prazosin, the effect of clonidine was not exhibited. Compared with prazosin, the selective antagonist of presynaptic adrenoreceptors, yohimbine, weakened the depressant effect of clonidine on emotional-behavioral nociceptive responses only very slightly. Meanwhile the adrenolytic drugs modified the behavior and hemodynamic components of the analgesic action of clonidine differently: The hemodynamic nociceptive responses were virtually unchanged after injection of prazosin, but significantly increased under the influence of yohimbine (Fig. 3).

The results of the neuropharmacologic analysis suggest different receptor mechanism for behavioral and hemodynamic effects of clonidine during pain. Inhibition of emotional behavioral nociceptive reactions under the influence of clonidine is realized through activation of brain adrenergic mechanisms through α_1-adrenoreceptors, whereas inhibition of the hemodynamic manifestations of the nociceptive response evidently takes place as a result of the action of clonidine on α_2-adrenoreceptors, as is shown by the definite dissociation between the effects of prazosin and of yohimbine on the emotional-behavioral and cardiovascular effects of the drug. This hypothesis also is confirmed by data showing an equal decrease in the intensity of nociceptive responses of BP under the influence of clonidine in both analgesic and subanalgesic doses, for with a decrease in the dose of clonidine its selectivity of action on α_2-adrenoreceptors is enhanced [6].

Opioidergic systems thus do not have the dominant role in the realization of the analgesic action of clonidine. This effect, manifested as inhibition not only of emotional-behavioral, but also of hemodynamic nociceptive responses, is connected much more closely, in our view, with its action on processes of adrenergic mediation. The experimental results described above also provide a basis in our view, for a new hypothesis on the functional heterogeneity of receptor substrates participating in the realization of hemodynamic and emotional-behavioral manifestations of the analgesic action of clonidine.

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ACTION OF ALCOHOL ON RATS WITH CHRONIC EMOTIONAL-PAINFUL STRESS

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Data obtained recently have shown that a neurosis-like state arising in experimental animals as a result of chronic emotional-painful stress (EPS) is accompanied by the creation of hypoxic conditions in the brain [1, 5]. Chronic alcohol consumption by experimental animals is known to lead to morphological change in the brain [3] and to long-term disturbances of higher nervous activity [4] and also of neurotransmitter systems [9]. Meanwhile the antistress action of alcohol in experimental animals has been described [11, 14].

The aim of this investigation was to study the effect of chronic alcohol consumption on reactivity of the autonomic nervous system and on oxidative processes in the rat brain.

EXPERIMENTAL METHOD

Experiments were carried out on 30 noninbred male albino rats weighing 200-250 g. The state of chronic EPS was created by combined exposure to "white noise" and subsequent electrodermal stimulation coupled with flashes of light on a stochastic schedule [5] daily for 4 weeks. The animals were divided into four groups: 1) control (intact rats), 2) animals exposed to EPS, 3) animals receiving a 20% solution of ethanol after water deprivation, 4) animals subjected to EPS and consuming ethanol. The rats were given alcohol from the first day of EPS. Under these conditions the rats of group 3 consumed 2-2.5 g/kg alcohol per head (calculated as 100% ethanol) daily, whereas animals of group 4 received 30-40% more.

Before the beginning of exposure to stress and alcohol consumption, and after the end of these procedures, the animals' behavior was assessed in an open field test and the autonomic parameters were studied during functional loading by hypokinesia (the animals were kept in special tubes, restricting their movements, for 2 h). The heart rate (HR) was recorded by means of a piezoelectric crystal. The blood pressure (BP) was determined by the appearance of pulsed waves after constriction of the base of the tail with a cuff.

To determine the stage of stress, according to Selye's system, the relative weight of the internal organs (adrenals, spleen, thymus, heart, and brown fat) was calculated. The level of brain energy metabolism was

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