PHARMACOLOGY

NEUROPHYSIOLOGICAL MECHANISMS OF THE ANTIHYPERTENSIVE EFFECT OF CLONIDINE IN THE PRESENCE OF PAIN

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KEY WORDS: pain; hemodynamics; sympathetic activity; endogenous adaptive systems; clonidine.

Hemodynamic changes are an inseparable component of the response of the body to pain, and their correction is an important task in the relief of pain. It has recently been shown that cardiovascular nociceptive reactions are formed as a result of generalized activation of the sympathetic structures in different parts of the CNS, effected through endogenous adaptive mechanisms, namely the antinociceptive systems of the brain and baroreceptor reflexes, which maintain coordination between the nutritive blood flow and the level of activity of the skeletal muscles [2]. Meanwhile it has been shown that opiates and opioids can disturb the link between sympathetic activity and motor activity and can lead to enhanced sympathetic and hemodynamic manifestations of pain against the background of analgesia [2, 6, 7]. At the same time it has been shown that ventral adrenomimetic agents – clonidine, levodopa, etc. – have a similar depriming action on reactions of different modalities, including hemodynamic nociceptive reactions. A detailed neurochemical analysis has been made of the mechanisms of their antihypertensive effect, and its nonopiate nature has been proved [2, 5]. However, the neurophysiological mechanisms of the hemodynamic effect of adrenomimetic agents in pain remain virtually unstudied.

This paper describes the study of the effect of clonidine, in analgesic doses, on baroreflex modulation of sympathetic tone and its descending antinociceptive control, factors which determine nociceptive changes in the circulation.

EXPERIMENTAL METHOD

Experiments were carried out on 12 conscious and 18 unanesthetized, curarized cats. As a first step, under ether anesthesia electrodes were implanted to stimulate the common peroneal nerve and (stereotactically) the central gray matter of the midbrain, and catheters were introduced into the carotid artery and jugular vein [3, 4]. Under chronic experimental conditions changes in arterial blood pressure (BP) and intersystolic intervals (ISI) caused by nociceptive stimulation of the peroneal nerve (10-15 V, 1 msec, 10-20 stimuli/sec) were studied during stimulation of the midbrain and activation of baroreceptors by artificially raising BP with phenylephrine [1, 4]. The parasympathetic baroreflex was evaluated by means of the coefficient of regression, reflecting correlation between lengthening of ISI and the increase in systolic BP. Electrical activity in the renal nerve (retroperitoneal approach) and sympathetic baroreflex also were investigated in acute experiments (the latter by recording the duration of inhibition of sympathetic activity in response to injection of phenylephrine). Parameters were recorded on the K-121 oscilloscope, followed by synchronous analysis and recording of the results by means of a computer system of our own design, based on the "Élektronika D3-28 [1]. Drugs were injected intravenously (in mg/kg) and intrathecally (in μg) at the L_2 level [8]: clonidine (from Boehringer, Germany – 0.05-0.5 mg/kg and 100-1000 μg; naloxone (Narcon, from "Endo," USA) – I mg/kg and 100 μg, and phentolamine ("Sandoz," Switzerland) – 1 mg/kg and 100 μg.

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TABLE 1. Effect of Clonidine on Parameters of Systemic Hemodynamics, Electrical Activity in Renal Nerve and Their Changes in Unanesthetized Cats in Response to Pain

Parameter recorded		Control	Clonidine (intravenously) mg/kg			
			0,05	0,1	0,25	0,5
Background	Amplitude of sympathetic activity, μV					
	Frequency of sympathetic activity, spikes/sec	30,6±3,1	19,4±2,8*	20,3±6,3*	13,3±1,7*	14,5±3,1*
	Blood pressure, mm Hg	43,6±7,6	52,5±9,1	19,0±3,0*	15,3±1,1*	20,4±1,7*
	Intersystolic intervals, msec	108±4	73±6*	85±3*	110±2	99±3*
	Coefficient of regression°, msec/mm Hg	305±9 12,6±3,4	400±29* 18,7±2,8*	621±81* —	810±142* 21,3±4,1*	902±50* —
	Duration of inhibition of sympathetic activity, sec	61±14	74±12	—	81±16	—
Exposure to nociceptive stimulation	Amplitude of sympathetic activity, μV	80,5±9,2	65,0±4,9	80,2±14,7	43,3±7,8*	50,6±10,2*
	Frequency of sympathetic activity, spikes/sec	124,1±13,3	122,1±9,5	17,0±8,6*	48,3±7,8*	41,5±14,4*
	Rise of blood pressure, mm Hg	73±5	77±4	50±8*	37±2*	43±3*
	Coefficient of regression°, msec/mm Hg	9,5±3,9	14,3±2,8	—	15,1±3,4	—
	Duration of inhibition of sympathetic activity, sec	51±12	60±11	—	73±12	—

Legend. °) Experimental results obtained on waking cats; *$p < 0.05$ compared with control.

EXPERIMENTAL RESULTS

In response to peroneal nerve stimulation, inducing a whole range of generalized affective manifestations of pain in conscious animals [3], marked hypertension and tachycardia developed. The amplitude and frequency of electrical activity in the renal nerve increased considerably (Table 1).

Just as in previous investigations [1, 2, 5] clonidine, in doses of 0.1-0.5 mg/kg, in which it caused dose-dependent inhibition of nociceptive reactions and responses of spinal neurons to pain stimuli, distinctly reduced pressor effects and tachycardia. In these same doses clonidine reduced the frequency and amplitude of sympathetic discharges during peroneal nerve stimulation (Table 1). Clonidine, injected intrathecally in doses of 100-200 μg, did not change, whereas in doses of 500-1000 μg, it progressively reduced the hemodynamic changes and bioelectrical responses due to pain (Fig. 1). The effects of clonidine were not altered by naloxone but were virtually abolished by phentolamine, after intravenous and intrathecal injection of both.

It is striking that the effect of clonidine on background levels of the hemodynamics and bioelectrical activity was reversible by naloxone and that its direction depended on the dose of clonidine (Table 1). For instance, in doses of 0.5-0.1 mg/kg clonidine depressed BP, but after administration in doses of 0.25-0.5 mg/kg, against the background of further inhibition of sympathetic activity and lengthening of ISI, BP was restored.

In conscious cats stimulation of the midbrain with a strength of 150-200 μA, leading to significant inhibition of emotional-affective reactions to peroneal nerve stimulation, was accompanied by a rise of BP by 30-60 mm Hg When injected intravenously in analgesic doses clonidine did not affect the changes in BP due to activation of the midbrain. After intrathecal injection of clonidine in doses of 200 and 500 μg into unanesthetized, curarized animals, responses of BP and changes in bioelectrical activity actually showed a tendency to increase (Fig. 1).

In doses of 0.05-0.1 mg/kg, causing a fall of BP, clonidine significantly increased the coefficient of linear regression in conscious animals (Table 1). This parameter, which directly reflects the sensitivity of the parasympathetic component of the baroreflex, was progressively increased even after injection of clonidine in doses of 0.25-0.5 mg/kg, in which it caused an increase in BP. During nociceptive stimulation of the peroneal nerve, weakening of the baroreflex coupled with pressor reactions and tachycardia took place. Under these conditions clonidine led to a very small reduction in the depressant effect of nociceptive stimulation on the baroreflex, although the general tendency remained for the baroreflex to be inhibited in response to nociceptive stimuli.

In experiments on unanesthetized cats clonidine, in analgesic doses, had no significant effect on the duration of the period of inhibition of electrical activity in the renal nerve, when BP was raised by phenylephrine, and it did not change this parameter during nociceptive stimulation of the peroneal nerve (Table 1).

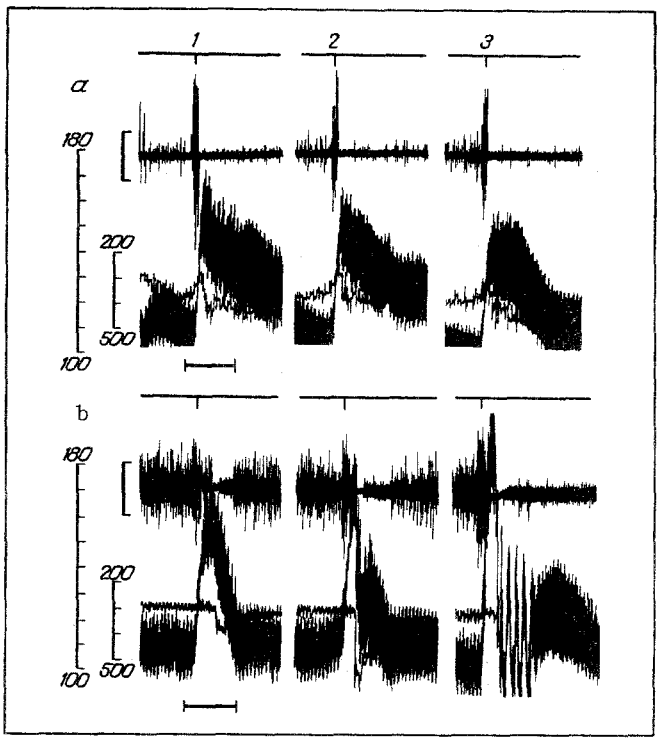

Fig. 1. Blood pressure, intersystolic intervals, and sympathetic activity during stimulation of peroneal nerve (a) and midbrain (b) after intrathecal injection of clonidine into unanesthetized cats: 1) control, 2) clonidine (200 ng), 3) clonidine (500 μg). From top to bottom: electrical activity in renal nerve, intersystolic intervals, blood pressure. Calibration: 200 μV, 20 sec.

The results showed that during pain BP is regulated by the direct central inhibitory effect of clonidine on sympathetic activity, as shown by the simultaneous inhibition of nociceptive changes in BP and changes in electrical activity in the renal nerve under the influence of the adrenomimetic drug. This fact distinguishes clonidine, in principle, from opiates and opioids which, in analgesic doses, have an activating action on the sympathetic system and lead to generalization of vasomotor reflexes over the system of propriospinal connections of the spinal cord [2].

As already mentioned, clonidine, when injected intrathecally, inhibited nociceptive changes of BP and sympathetic activity only in doses of 500 μg and over, whereas, after its intravenous injection, even in a dose of 0.1 mg/kg (100 μg/kg), hypertensive nociceptive reactions were significantly reduced and were not reversible by naloxone. Hence it will be evident that the depressant effect of clonidine on the sympathetic system during pain is realized through adrenergic mechanisms, but it is formed only to an insignificant degree at the segmental level of vasomotor regulation.

Inhibition of sympathetic activity which, on the one hand, determines the antihypertensive effect of clonidine during pain, and, on the other hand, its hypotensive action (i.e., lowering of the background BP), is evidently realized through similar neurochemical systems. For instance, unlike inhibition of hypertensive nociceptive reactions, a role of considerable importance in the hypotensive action of clonidine may be played by opioidergic mechanisms.

The investigations also showed that the antihypertensive action of clonidine in pain is unconnected with any changes in modulating influences of endogenous homeostatic systems. The fact that identical results were obtained by parenteral and intrathecal injection of clonidine suggests that it does not weaken descending sympathetic activating effects of antinociceptive structures of the midbrain and does not prevent their realization at the spinal cord level. The hemodynamic action of clonidine in pain is likewise unconnected with baroreflex parasympathetic and sympathetic regulation of the circulation, for the drug did not change the tendency toward inhibition of baroreflexes under the influence of nociceptive stimulation.

LITERATURE CITED

1. E. G. Bogdanov, Author's Abstract of Dissertation for the Degree of Candidate of Medical Sciences, Leningrad (1987), p. 15.
2. V. A. Mikhailovich and Yu. D. Ignatov, (ed.), The Pain Syndrome [in Russian], Leningrad (1990).
3. Yu. N. Vasil'ev and Yu. D. Ignatov, Farmakol. Toksikol., No. 6, 676 (1978).
4. A. V. Dmitriev, Neuropharmacological Aspects of Pain [in Russian], Leningrad (1982), pp. 95-108.
5. A. A. Zaitsev, Current Problems in Pain Relief by Drugs [in Russian], Leningrad (1988), pp. 62-74.
6. N. A. Osipova, Evaluation of the Effect of Narcotic, Analgesic, and Psychotropic Drugs in Clinical Anesthesiology [in Russian], Leningrad (1988).
7. F. Freye, Opioid Agonists, Antagonists, and Mixed Narcotic Analgesics, Springer-Verlag, Berlin (1987).
8. R. H. W. M. Hoogen and F. C. Colpaert, Pharmacol. Biochem. Behav., **15**, 515 (1981).

NORMALIZING EFFECT OF ANTIDEPRESSANT IMIPRAMINE ON CHANGES IN CIRCADIAN MOVEMENT PATTERN OF PINEALECTOMIZED RATS AFTER A CHANGE IN TIMING OF THE PERIOD OF DAYLIGHT

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The ability of antidepressants to interfere with the function of the pineal gland has been noted and is recognized as an important element of the psychotropic activity of these substances [1, 3]. Most studies of this type have been carried out by the use of biochemical methods, and for that reason they have left mainly unanswered the question of to what degree the changes taking place involve the specific properties of the gland. In the modern view the pineal gland above all adjusts the various physiological processes to external environmental conditions changing in accordance with the duration of the photoperiod [7].

In this investigation the effect of an antidepressant was studied on disturbances of adjustment of the circadian rhythm of motor activity of rats following a shift of several hours in the time of the photoperiod in animals after pinealectomy.

EXPERIMENTAL METHOD

Experiments were carried out on 40 noninbred male and female albino rats weighing 220-280 g. The circadian rhythm of spontaneous motor activity was studied in an actograph, whereby the number of journeys made by the animal around its individual cage (30 × 12 × 12 cm) could be recorded continuously. Each journey was recorded graphically on a moving paper tape, as a result of which an actogram covering a period of several days was obtained. It was divided into equal 3-hourly sections and the number of journeys in these areas was counted. The results were used to construct individual chronograms. For overall assessment of the results the mean values of motor activity were counted during the same time cuts for the group of animals. Cosinor analysis was carried out, with the construction of confidence ellipses for the group

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