EFFECT OF VERAPAMIL ON BEHAVIORAL AND MICROCIRCULATORY DISTURBANCES IN PAIN SYNDROME OF SPINAL ORIGIN

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A generator of pathologically enhanced excitation (GPEE) has been shown [2] to be the essential mechanism of central pain syndromes. Calcium channel blockers inhibit hyperactivation of neurons [14] and foci of epileptic activity [1], which are one form of GPEE.

The facts described above suggest that calcium channel blockers may have a corrective influence on the onset and development of central pain syndromes.

The aim of the present investigation was to study the role of the calcium channel antagonist verapamil, and also a combination of verapamil with the analgesic drug analgin in alleviation of a pain syndrome of spinal origin (PSSO) and eradication of microcirculatory disorders induced by it.

EXPERIMENTAL METHOD

Experiments were carried out on 120 male Wistar rats weighing 200-250 g. A PSSO was induced in rats by creating a GPEE in the posterior horns of the lumbar region of the spinal cord on the right side by application of an agar wafer containing penicillin (the Na salt). A detailed account of the investigation of behavioral responses and the microcirculation was given previously [3]. Verapamil (Finoptin) was obtained from "Orion" (Finland) in doses of 1.25 and 0.125 mg/kg; analgin*, in doses of 150 and 15 mg/kg, and also a combination of verapamil (1.25 mg/kg) and analgin (150 mg/kg) were used. The preparations were injected intravenously 30 min after application of the wafer. Biomicroscopy was carried out 60 min after creation of the GPEE, and experiments on the control rats were in accordance with the scheme given above, but physiological saline was given instead of the drugs.

Since after systemic administration of calcium channel blockers, it is difficult to decide whether its effect is connected with activation of antinociceptive structures and/or with their direct action on neuronal processes in GPEE, a special series of experiments was carried out in which verapamil was applied in an agar wafer to the dorsal surface of the spinal cord actually in the region of GPEE.

In each series of experiments 10 animals were used. The significance of differences was determined by Student's test.

*1-phenyl-2,3-dimethyl-5-pyrazolone-4-methylaminomethanesulfonate sodium.

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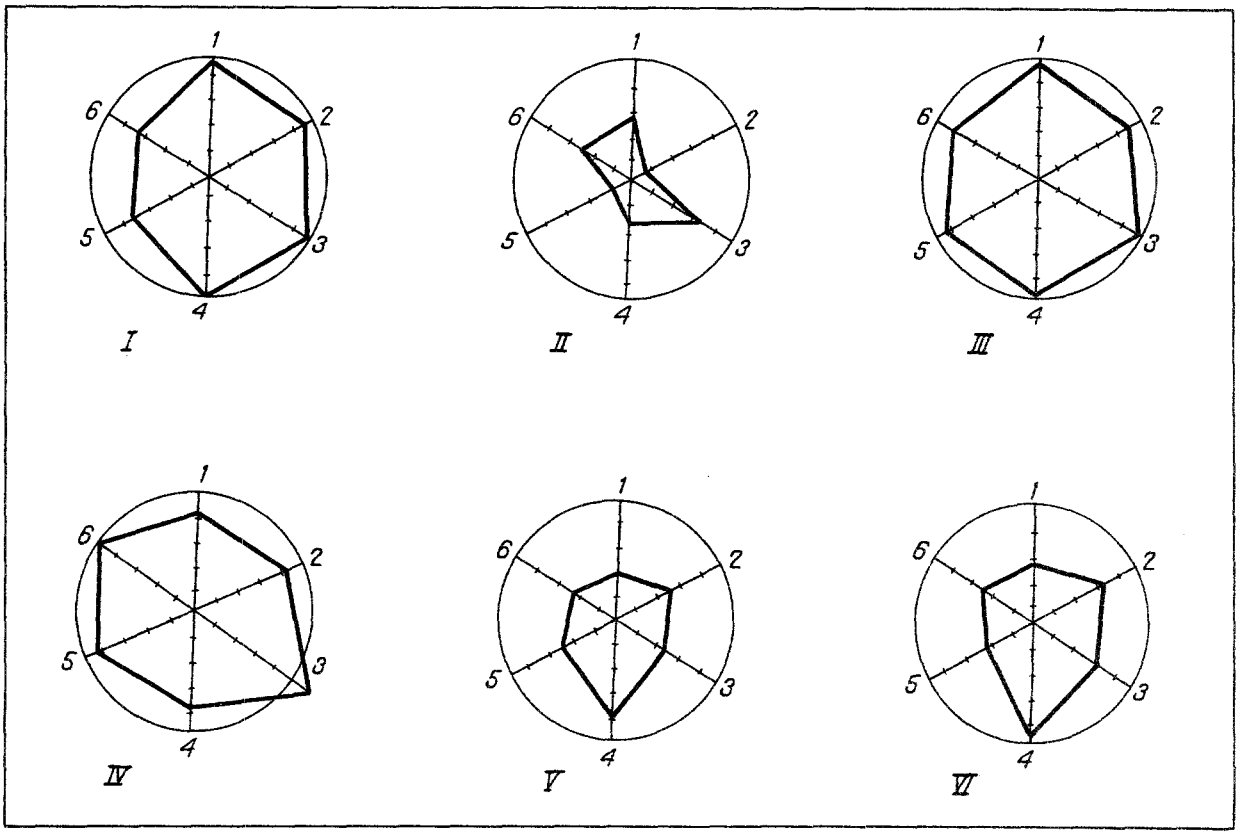

Fig. 1. Changes in behavioral components of PSSO after injection of verapamil. Intensities of components of PSSO indicated quantitatively on linear-circular diagrams: 1) vocalization, 2) general motor reaction, 3) local reaction, 4) episode in response to provocational stimulus, 5) frequency of spontaneous episodes, 6) duration of spontaneous episodes. Center of circle is origin of ordinate, radius of circle is ordinate of one component, intensity of each component expressed as percentages of initial value. Here and in Fig. 2: I) 0.9% NaCl, II, III) verapamil (1.25 and 0.125 mg/kg, respectively), IV) analgin (150 mg/kg, V) verapamil (1.25 mg/kg) + analgin (150 mg/kg), VI) verapamil in wafer.

EXPERIMENTAL RESULTS

As was shown previously [3] PSSO is manifested as characteristic behavioral responses: vocalization, a general motor response, a local response in the form of licking the paw, combing and biting certain areas of that paw, and spontaneous and induced paroxysms of pain, and was accompanied by disturbances of the microcirculatory system, including slowing of the blood flow in the venules, aggregation of erythrocytes, plasmatization, increased contractility of the lymphatic microvessels, increased degranulation of mast cells, and increased venular permeability.

Verapamil in a dose of 1.25 mg/kg essentially weakened the behavioral components of the PSSO. The intensity of vocalization and of the general motor response during the period of an attack of pain was reduced by more than 40% and a local response was almost absent (Fig. 1).

Before injection of verapamil, application of nonnociceptive stimulation to the right paw of animals with PSSO provoked a strong attack of pain, and after injection of verapamil the intensity of the evoked attack was reduced by 30%. The frequency and duration of spontaneous pain episodes were significantly reduced. In the smaller dose (0.125 mg/kg) verapamil had no effect.

Intravenous injection of analgin in a dose of 150 mg/kg against the background of PSSO caused a very small decrease in only some of the components of PSSO. Combined injection of verapamil and analgin did not lead to potentiation of the analgesic effect (Fig. 1).

TABLE 1. Microcirculatory Disturbances in PSSO and after Injection of Verapamil and Analgin

Drugs associated with PSSO	Intensity of microhemocirculatory disturbances, %										Venular permeability				
	slowing of blood flow in venules	aggregation of erythrocytes		extravasation of erythrocytes from venules	stasis	plasmatic vessels	pavementing of leukocytes	number of mesenteric windows, % of total number			Number of rats with various degrees of labeling, % of total number of rats in experiment				
		capillaries	venules					without label	1-10 labeled vessels	over 10 labeled vessels	0	I	II	III	IV
0.9% NaCl (control)	100	60	100	40	70	100	90	64	27	9	0	100	100	100	80
Verapamil, 1.25 mg/kg	10*	10*	0*	10	0*	10*	50*	90*	4*	6*	60*	40*	40*	20*	10*
Verapmil, 0.125 mg/kg	80	40	40	20	100	80	80	72	20	6*	0	100	100	100	50*
Analgin, mg/kg	100	80	80	30	80	80	80	63	37	0*	0	100	100	100	71
Veramamil, 1.25 mg/kg + analgin, 150 mg/kg	30*	10*	0*	0	0*	20*	20*	90*	8*	2*	70*	40*	40*	10*	0*
Verapamil in water	50*	10*	20*	10	10*	20*	70	93*	4*	6*	60*	40*	40*	20*	10*

Legend. *$p < 0.05$ compared with control.

The study of the action of verapamil and analgin on the state of the microcirculation in rats without PSSO showed that analgin did not affect the state of the terminal blood flow, venular permeability, mast cells, or lymphatic microvessels. Verapamil (1.25 mg/kg) increased the velocity of the blood flow in the venules and reduced the intensity of pavementing of the leukocytes in the venules; it also induced dilatation of the arterial and venular microvessels and reduced contractility of lymphatic microvessels. Injection of a mixture of analgin and verapamil had the same action.

Injection of verapamil in a dose of 1.25 mg/kg into rats with PSSO led to a significant decrease in the number of animals with slowing of the blood flow in the venules, aggregation of erythrocytes, plasmatization, and stasis. Reducing the dose of the drug by 90% did not lead to a normalizing effect on the microcirculation. Injection of analgin in association with the development of PSSO did not affect the state of the terminal blood flow. Combined injection of verapamil and analgin had an action similar to verapamil alone on the terminal blood flow (Table 1).

Injection of verapamil (1.25 mg/kg) and a mixture of verapamil and analgin significantly reduced the extent and intensity of disturbances of venular permeability for particles of colloidal carbon. The use of verapamil (0.125 mg/kg) and of analgin (150 mg/kg) had the same action to a limited degree (Table 1). Verapamil (1.25 mg/kg) and a mixture of verapamil and analgin significantly reduced degranulation of mast cells induced by PSSO, analgin (150 mg/kg) increased it, whereas verapamil (0.125 mg/kg) and analgin (15 mg/kg) together had no effect on these parameters (Fig. 2).

The frequency of contractions of the walls of the lymphatic microvessels (80-100 μm) was unchanged after injection of analgin (150 mg/kg) and was significantly reduced (in some cases completely stopped) by injection of verapamil (1.25 and 0.125 mg/kg) and also of a mixture of verapamil and analgin (Fig. 2).

As a result of the direct action of verapamil on the region of GPEE in the dorsal horns of the spinal cord, just as after intravenous injection, the intensity of spontaneous episodes was significantly reduced (Fig. 1), and parameters of the microcirculatory system were improved (Fig. 2).

Normalization of behavioral responses and of the microcirculation may be linked with the direct action of the drugs on hyperactivity of neurons of GPEE.

The results relative to suppression of pathological pain by verapamil are in agreement with others [6] showing inhibitor effects of calcium channel blockers on models of visceral pain, but they differ from investigations [4, 8, 10], in which no analgesic effect of calcium channel blockers could be found by the hotplate test.

The difference between our investigations and those cited above is that the effects of verapamil were studied on a model of pathological pain, whereas the authors cited studied the effects of calcium channel antagonists on models of physiological pain, i.e., under conditions when the nervous system was functioning normally. Calcium channel antagonists may be ineffective in depressing calcium currents in neuronal membranes under normal conditions, but their effect may be exhibited under pathological conditions. For instance, it has been shown on cerebral cortical neurons [12] that verapamil, which did not affect mediator release under normal conditions, blocked mediator release in low doses during activation of calcium channels.

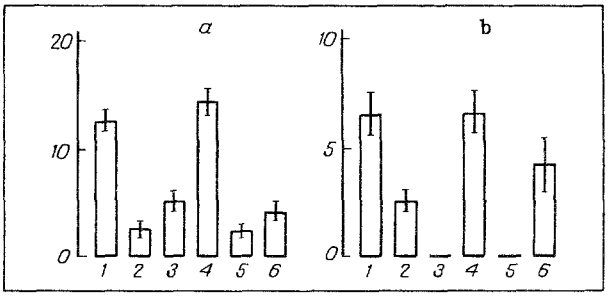

Fig. 2. Degranulation of mast cells (a) and contractility of lymphatic microvessels (b) during PSSO and after injection of verapamil and analgin. a: Ordinate, degranulated mast cells (in %), b: ordinate, number of contractions of lymphatic microvessels (in min).

Data on the opiate activity of calcium channel blockers are interesting. It has been shown [9] that calcium channel antagonists have a significant action on the endogenous opioid system, and that injection of calcium channel blockers potentiates and prolongs the antinociceptive effect of opioids [4, 5, 8, 9]. The action of verapamil on PSSO may also be effected through the opiate component of the antinocicpetive system.

Finally, one possible mechanism of the normalization of disturbances associated with PSSO is the action of verapamil on the microcirculatory system. It has now been shown that preparations of this group have a dilator effect on microvessels and reduce venular permeability in control animals [11], and also depress permeability for macromolecules and reduce degranulation of mast cells under pathological conditions [13, 15]. Our results correlate with those of investigations described above. Verapamil [7] was found not to affect the splanchnic and central hemodynamics, so that the drug may be considered to have a direct action of hyperactive neurons of GPEE in the present experiments.

Thus the positive action of verapamil during PSSO is linked both with its ability to reduce the severity of this syndrome by weakening hyperactivity of the neurons of GPEE and with the direct effect of the drug on components of the microcirculatory system.

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