# ANTINOCICEPTIVE EFFECT OF SEROTONIN

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KEY WORDS: serotonin; antinociceptive action; methysergide; naloxone.

Processes taking place in the CNS with the participation of serotonin play an important role in the functioning of natural antinociceptive mechanisms and also in the mechanisms of the analgesic action of morphine [2, 4, 8, 10, 11, 13, 14]. This conclusion is based on the results of experimental studies in which the course of serotoninergic processes was altered in various ways: by destruction or stimulation of structures containing serotoninergic neurons, by administration of drugs affecting serotonin metabolism in the brain or synaptic transmission in serotoninergic neurons.

In the present investigation the effect of serotonin, when injected by the intraventricular route, on the threshold of the nociceptive vocalization response to electrical stimulation of the tissues of the tail was studied in rats. The serotonin was injected in this way because it does not readily pass through the blood–brain barrier.

## EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 250-350 g. The animals were anesthetized with halothane and a cannula was implanted in the left lateral ventricle in accordance with coordinates from De Groot's stereotaxic atlas. The cannula, which was a hollow steel needle, was secured to the animal's skull with acrylic glue, applied to a wire framework. The experiments began 7-10 days after the operation. The base of the tail was stimulated through needle electrodes by single square pulses 0.1-0.5 msec in duration. The minimal voltage of the pulses to cause the animals to respond with a squeak was determined. The results were assessed in alternative form. Intervals between the experiments were at least 3 days and each animal was used in the experiments not more than 3 times. Serotonin was given as the creatinine sulfate in isotonic sodium chloride solution. The serotonin solution was injected through the cannula into the lateral ventricle in doses of 50-160 $\mu$g, always in the same volume (10 $\mu$l).

Morphine hydrochloride (5-10 mg/kg) and naloxone (2 mg/kg) were injected subcutaneously and methysergide (0.5 mg/kg) intraperitoneally.

At the end of the series of experiments the animals were killed and the position of the tip of the cannula determined. Altogether 29 rats were used.

Significance of the results was assessed by Student's t-test.

## EXPERIMENTAL RESULTS

After injection of serotonin into the lateral ventricle of the rats a dose-dependent effect of elevation of the threshold of the vocalization response to electrical stimulation of the animal's tail was observed (Figs. 1 and 2). The animals under these circumstances were still able to squeak spontaneously. The most marked effect was observed 5-15 min after injection. The analgesic action of the drug continued for 25-30 min. In the intensity of its analgesic effect serotonin in a dose of 160 $\mu$g corresponded to morphine given in doses of 5-10 mg/kg subcutaneously. Injection of isotonic solution into the cerebral ventricles in a volume equal to that of the serotonin solution led to no change in the nociceptive response.

Methysergide, which blocks serotonin receptors, in a dose of 0.5 mg/kg intraperitoneally had no effect on the threshold of the animals' vocalization response (Fig. 2C). However, injection of methysergide 1 h before injection of serotonin prevented elevation of the threshold of the nociceptive response by serotonin (Fig. 2D).

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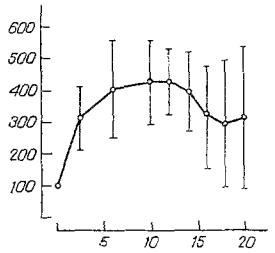


Fig. 1

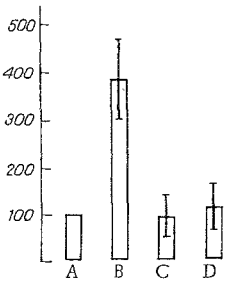


Fig. 2

Fig. 1. Effect of serotonin (160 μg, into the lateral ventricle) on threshold of vocalization response in rats. Abscissa, time (in min) after injection of serotonin; ordinate, threshold of nociceptive response (in %, threshold of response before serotonin taken as 100%).

Fig. 2. Threshold of vocalization response in rats (in %) before injection of serotonin (A), after injection of 160 μg serotonin into lateral ventricle (B), after intraperitoneal injection of methysergide in a dose of 0.5 mg/kg (C), and after injection of serotonin, 160 μg, into lateral ventricle preceded 1 h beforehand by intraperitoneal injection of 0.5 mg/kg methysergide (D). Threshold of response before injection of serotonin taken as 100%.

Like methysergide, the morphine antagonist naloxone (2 mg/kg, subcutaneously) did not change the threshold of the vocalization response in the animals. Naloxone, injected 3 min after serotonin, did not affect its antinociceptive action. A control series of experiments showed that under the same experimental conditions naloxone abolished the analgesic effect of morphine (10 mg/kg, subcutaneously) 5 min after injection.

The results of these experiments show that serotonin, when injected into the lateral ventricle, has a marked antinociceptive action, manifested as a considerable rise in the threshold of the vocalization response of the animals to electrical stimulation of the tail. The fact that the animals were still able to squeak spontaneously is evidence of definite selectivity in the action of serotonin. The ability of methysergide, which blocks serotonin receptors, to prevent the antinociceptive action of serotonin is evidence that this effect of serotonin is the result of its action in serotoninergic synapses.

The inability of naloxone to abolish the antinociceptive effect of serotonin indicates that the analgesic action of serotonin is effected in this case, evidently, without involvement of the system of brain opiate receptors. Similar results were obtained by submeningeal application of serotonin at the spinal cord level and by systemic administration of naloxone [12, 14].

The antinociceptive effect of serotonin when injected into the cerebral ventricles may take place through strengthening of descending inhibition of the segmental nociceptive "input." The morphological substrate for the inhibitory system may be projections from the posterior group of raphe nuclei (n. raphe magnus, n. raphe obscurus, n. raphe pallidus), containing serotoninergic neurons, to neurons of the posterior horns of the spinal cord [3, 9]. However, according to data in the literature [6], serotonin does not affect unit activity of the raphe nuclei when applied iontophoretically. Meanwhile, after microinjections of serotonin into the ventral part of the periaqueductal gray matter, a marked antinociceptive effect not abolished by microinjections of naloxone into the same structures is observed [1]. Consequently it seems more likely that serotonin, injected into the ventricles, affects the structures of the periaqueductal gray matter. These structures participate in the function of the natural antinociceptive system and may have an inhibitory influence on neurons of the posterior horns of the spinal cord through the system of raphe nuclei [7]. Moreover, through interaction between serotonin and structures of the periaqueductal gray matter, ascending antinoceptive influences may be potentiated [1].

Serotonin has a marked antinociceptive effect when injected beneath the spinal meninges on account of its direct influence on the segmental apparatus [12, 14]. Accordingly the direct action of serotonin, when injected into the ventricles, on interneuronal transmission in the spinal cord cannot be ruled out.

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# EFFECT OF NONACHLAZINE ON BRAIN AND MYOCARDIAL NORADRENALIN LEVELS IN NORMAL AND STRESSED RATS


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KEY WORDS: nonachlazine; noradrenalin level; brain stem; myocardium; stress reaction.


Disturbances of neuromediator and, in particular, of catecholamine metabolism during the stress reaction are confirmed by the results of many investigations. Considerable changes in the noradrenalin concentration in the hypothalamus, adrenals, heart, and blood during stress lead to significant disturbances of function of sympathetic regulation of the activity of the cardiovascular system [1, 2, 7, 14]. Changes in catecholamine metabolism also have been observed in patients with ischemic heart disease and myocardial infarction [8, 11, 13].

In connection with the facts described above it was decided to investigate the effect of the new antianginal drug nonachlazine, which acts upon adrenergic processes [5], on the brain and heart noradrenalin levels under normal conditions and during neurogenic stress.

## EXPERIMENTAL METHOD

Experiments were carried out on 60 sexually mature rats weighing 200-250 g. The noradrenalin level in the brain stem and myocardium was determined by the modification in [9] of the fluorometric method [12].

There were four series of experiments. In the experiments of series I (control) the noradrenalin level was determined in the brain tissue and myocardium of intact rats. In the experiments of series II the noradrenalin level in the tissues was determined 15 and 30 min after intravenous injection of nonachlazine in a dose of 10 mg/kg. In series III the noradrenalin level was studied 30 min after the beginning of electrical stimulation of the thigh through bipolar subcutaneous electrodes (10 V, 0.5 msec, 20 stimuli/sec, for 10 sec with intervals of 5 min) while the rats were immobilized. In series IV the noradrenalin level was determined in the brain stem and heart 30 min after injection of nonachlazine and electrical stimulation of the animals. During the period of development of the stress reaction changes in the ECG were recorded in standard lead II. The experimental results were subjected to statistical analysis with a $P < 0.05$ level of significance.


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