ling syndrome. In the other rabbits, the most marked state of seizure preparedness was at times of maximal excess of the number of SIS in the hippocampus over their number in the cortex. With a decrease in this gap the fits became shorter in duration, with no more than one or two stages [7], or they ceased completely (Fig. 4). The number and duration of the seizure discharges also diminished or they disappeared. In this case also, to restore the kindling syndrome it was necessary to increase the strength of the stimulating current, and this led to an increase in the number of SIS in the hippocampus and to synchronization of cortical spikes with them.

The results thus provide conclusive evidence that an independent and powerful focus of hyperactivity can be formed in response to kindling stimulation of the rabbit hippocampus, not only in the zone of stimulation and in other deep brain formations, but in the cerebral cortex also. If the secondary cortical focus of hyperactivity remains dependent on the primary hippocampal focus and "obeys" it, development of the kindling syndrome is undisturbed. If, however, such a focus acquires the properties of an autonomous focus, independent of the hippocampal focus, it may depress activity of the primary focus and inhibit the formation of the kindling syndrome. Data on the development of intracentral and central-peripheral relations obtained in the course of kindling stimulation will enable the neurophysiological responses under the influence of ionizing radiation on the CNS to be studied more deeply in future research.

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ROLE OF MONOAMINE SYSTEMS IN MECHANISMS OF REGULATION OF ANALGESIA IN SOME TYPES OF REFLEX STIMULATION

E. O. Bragin, N. N. Batueva, and R. A. Durinyan

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Investigations of analgesia during the action of opiates [2-7, 9, 10, 12, 13] or electrical stimulation of different regions of the brain [2, 5, 8] have demonstrated the important role of monoamine systems. Depression of synthesis of noradrenalin (NA), dopamine, or serotonin (5-HT) by means of various pharmacologic inhibitors modifies sensitivity to pain under these influences, and restoration of the amine level by administration of their precursors causes recovery of the analgesic effect.

It can be postulated that monoamine systems also play an important role in the regulation of pain during the action of auricular electroacupuncture (AEA) or stress. It was accordingly decided to carry out a series of experiments to study the role of monoaminergic systems in the mechanisms of regulation of pain sensitivity during the action of these stimuli.

Central Research Institute of Reflex Therapy, Moscow.

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TABLE 1. Effect of α-MPT, Propranolol (P), and Haloperidol (H) on Dynamics of Latent Periods of HP and TF Tests (in percent of initial values) before and after Stress and AEA

Experimental conditions	Initial value, sec	Time after procedure, min					
		0	5	10	20	30	40
HP							
physiological saline + stress	11,2±0,8	220*	193	—	—	—	—
α-MPT + stress	10,9±0,8	252*	206	—	—	—	—
TF test							
physiological saline + stress	3,5±0,2	220*	100	—	—	—	—
α-MPT + stress	3,6±0,4	214*	169	—	—	—	—
HP							
physiological saline + AEA	9,0±0,9	145*	160*	126*	144*	141*	128*
α-MPT + AEA	10,3±1,0	117	155*	138	118	137*	141
TF test							
physiological saline + AEA	2,7±0,2	148*	140*	133*	144*	133*	111
α-MPT + AEA	3,1±0,3	135*	132*	122*	112*	106†	106
HP							
physiological saline + AEA	8,4±1,1	253*	203*	232*	239*	171*	—
propranolol + AEA	8,9±1,4	133*	100†	103†	100†	98	—
propranolol alone	8,8±1,4	133	106	120	120	108	—
HP							
physiological saline + stress	10,3±1,4	540*	442*	—	520*	417*	—
haloperidol + stress	10,4±0,9	521*	360†	—	257†	233†	—
TF test							
physiological saline + AEA	5,2±0,7	215*	—	180*	155†	142†	—
haloperidol + AEA	5,6±0,7	200*	—	137*	120	110	—

Legend. Here and in Table 2: *P < 0.5 compared with initial value, **P < 0.05 for comparison between control and experiment.

EXPERIMENTAL METHOD

Experiments were carried out on 129 albino rats weighing 200-270 g. Sensitivity to pain was assessed by the latent period (LP) of the hot plate (HP) and tail-flick (TF) tests [1, 8]. As reflex stimuli, electrical stimulation of the limb with a pulsed current of 2.5 mA, 8 pulses/min, pulse duration 2 sec, was applied for 3-10 min. AEA was carried out through electrode clips fixed to the concha auriculae in the region of the lung projection point, with a current of 0.6-1.0 mA, 4 Hz, 0.04 msec, 15-30 min.

Inhibition of catecholamine synthesis was induced by α-methylparatyrosine (α-MPT, 150 mg/kg, intraperitoneally, 4 h previously) and 5-HT synthesis was inhibited by parachlorophenylalanine (PCPA, 300 mg/kg intraperitoneally, 72 h previously). β-adrenoreceptor activity was inhibited by propranolol (5 mg/kg, intraperitoneally, 15 min previously), and dopamine receptor activity was inhibited by haloperidol (0.05 mg/kg intraperitoneally, 60 min previously). Control rats were given intraperitoneal injections of physiological saline. The NA and 5-HT levels were determined in brain and spinal cord tissues [4, 11, 14]. The results were analyzed by Student's t test for independent pairs or by the method of paired comparisons.

EXPERIMENTAL RESULTS

Data on the effect of α-MPT on LP of the HP and TF tests during the action of stress and of AEA are given in Table 1. (The experiments were carried out in collaboration with A. Pert and D. Massari, from the Laboratory of Pharmacology and Biochemistry, National Institute of Psychiatry, Bethesda, USA).

The initial LP of the HP and TF tests on animals of the experimental and control groups did not differ statistically significantly from one another. α-MPT also was found not to affect LP of the HP and TF tests during the recovery period in rats after exposure to mock stress (not shown). In animals exposed to stress (Table 1) significant lengthening of LP of the HP test to 250% (from 10.9 ± 0.8 to 27.5 ± 4.1 sec; P < 0.05) was observed after injection of α-MPT, and to 220% (from 11.2 ± 0.8 to 24.7 ± 3.5 sec; P < 0.05) in the control. By the 5th minute these parameters had fallen and did not differ significantly from their ini-

TABLE 2. Effect of PCPA on Dynamics of LP of HP and TF Tests (in percent of initial value) after Stress and AEA

Experimental conditions	Initial value, sec	Time after procedure, min				
		0	5	10	30	40
HP						
physiological saline + stress	11,7±1	268*	160*	—	—	—
PCPA + stress	12,6±1,5	191†	111	—	—	—
TF test						
physiological saline + stress	3,3±0,2	124*	100	<	—	—
PCPA + stress	3,5±0,3	120	110	—	—	—
HP						
physiological saline + AEA	8,4±0,7	157*	171*	167	144*	132
PCPA + AEA	7,5±1,3	161*	129†	110	126*	100
TF test						
physiological saline + AEA	2,3±0,1	160*	139*	104	113*	100
PCPA + AEA	2,6±0,2	111†	120	100	105	100

tial level ($P > 0.05$). Similar results also were obtained when LP of the TF test was measured (Table 1). Comparison of parameters between the groups after stress revealed no significant differences in LP of the HP and TF tests in rats receiving α-MPT or physiological saline.

AEA (Table 1) caused a significant increase in LP of the HP and TF tests throughout the duration of the experiment in rats of the control group. Significant lengthening of LP of the HP test compared with its initial value was found in the experimental animals only at the 5th and 30th minutes ($P < 0.05$). Statistical analysis of the results revealed no significant differences in the value of LP of the HP test between the experiment and control after AEA. It was shown by the TF test that AEA causes significant lengthening of its LP in rats receiving α-MPT, during the first 20 min. Statistical analysis showed that LP of the TF test in the experimental group was significantly shorter than in the control only at the 20th and 30th minutes.

Exhaustion of catecholamine neurons of the brain and spinal cord, and also in the peripheral nervous system, induced by α-MPT thus causes no change in activity of the analgesic systems during stress, whereas slight inhibition of those systems is observed during the action of AEA.

The possible explanation may be that during the action of intensive stress stimuli neurochemical systems with higher thresholds, not connected with catecholamine systems, may become activated and bring about high antinociceptive tone, whereas during AEA the intensity of the stimuli is evidently too low to produce complete activation of these systems.

In the next series of experiments the effect of the β-adrenoreceptor inhibitor propranolol on the HP test was studied in rats after AEA (Table 1). Propranolol, in a dose of 5 mg/kg, did not affect the initial values of LP of the HP test nor the values of its LP during 30 min after injection of the drug. AEA of the experimental animals did not lengthen LP of the HP test at any time during the experiment, whereas in the control rats after AEA a significant increase in LP of the HP test (compared with the experiment) was observed.

Data on the effect of the dopamine receptor inhibitor haloperidol on the duration of LP and the dynamics of the HP and TF tests before and after stress and AEA also are given in Table 1. Injection of haloperidol did not affect the initial value of LP of the HP test. For instance, the duration of LP was 10.4 ± 0.9 sec in the experimental rats and 10.3 ± 1.4 sec in the controls ($P > 0.05$).

Comparison of the results obtained after stress or AEA showed that in rats receiving the inhibitor responses to pain were significantly weaker in the later time intervals of the recovery period (after the 20th minute). These results indicate participation of dopamine receptors in the mechanisms of activation of the antinociceptive systems during stress and AEA; their functional significance, moreover, was manifested after a definite time interval. Meanwhile the presence of a marked analgesic effect immediately after the end of stress or AEA points to the participation also of other neurochemical systems unconnected with dopamine-dependent mechanisms.

Table 2 gives data on the effect of exhaustion of serotonin neurons on the HP and TF tests before and after stress or AEA. The initial values of the HP and TF tests in rats re-

ceiving PCPA or physiological saline did not differ statistically significantly from each other before stress.

Stress caused a significant increase in LP of the HP test in the experimental rats compared with the initial values and also an increase in LP of the HP and TF tests in the control rats. Comparison of the results between the groups showed that parameters characterizing sensitivity to pain were significantly lower in the experiment than in the control. A session of AEA on rats of the control group caused a definite increase, significant compared with the initial value, in LP of the HP test immediately after the end of stimulation and also at the 5th and 30th minutes. In the experimental rats LP of the HP test showed a marked tendency to increase during the first minutes after the end of AEA and it was significantly higher at the 30th minute than before it. Comparison of the values obtained for the two groups showed that in the experimental rats LP of the HP test was significantly less only at the 5th minute of the recovery period. Measurement of LP of the TF test showed that AE causes a significant increase in the results of this test practically throughout the experiment in the control rats, whereas in the experimental animals no significant increase was found compared with the initial level. Comparison of the results between the groups showed a significantly shorter value of LP of the TF test in the experimental rats at the first minute of the recovery period.

It will be clear from Table 2 that in animals receiving PCPA the 5-HT content was significantly reduced in brain and spinal cord tissues. The NA concentration did not change the results under these circumstances.

It can be concluded from these results that a decrease in activity of the serotoninergic systems of the body (central and also, perhaps, peripheral) leads to depression of the antinociceptive mechanisms, when activated by stress and AEA. Despite this, however, the analgesic effect of stress and AEA in animals with depressed 5-HT synthesis, was pronounced, indicating activation of other neurochemical mechanisms also, aimed at depressing sensitivity to pain.

The monoaminergic systems of the body thus participate in production of the analgesic effect of stress and AEA. Meanwhile activation of other neurochemical systems, independent of monoamines and whose function is aimed at reducing sensitivity to pain, is also observed.

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