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EFFECT OF SEROTONINERGIC AGENTS ON AVOIDANCE BEHAVIOR UNDER ACUTE STRESS

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KEY WORDS: serotonin; S_2 receptors; stress; behavior.

Activation of the serotoninergic system of the brain is accompanied by depression of behavioral responses [4, 6]. Conversely, a fall in the brain serotonin (5-HT) level correlates with increased motor reactivity and the performance of purposeless, superfluous responses [11]. However, in the initial stages of habit formation elevation of the brain 5-HT level reduces emotional hyper-reactivity and improves learning [2]. The role of the serotoninergic system in adaptation to emotional stress has not been adequately studied.

The object of this investigation was to assess the effect of drugs with serotonin positive and antiserotonin activity on realization of avoidance behavior in a stress situation under conditions of a relative deficiency of information on the method of avoidance.

EXPERIMENTAL METHOD

Male Wistar rats weighing 200-250 g, kept in cages, six animals in each cage, with free access to food and water, were used. Avoidance behavior was assessed by the method [10] in the modification [1]. All drugs were injected intraperitoneally in aqueous solutions. The following drugs were used: 5-hydroxytryptophan (5-HTP, from Serva, West Germany), zimelidine (provided by Professor Ross, from Astra), trazodone and m-chlorophenylpiperazine — CPP (provided by Professor Maj, Institute of Pharmacology, Polish Academy of Sciences, Cracow), pirenpiron (supplied by Professor R. Janssen, Janssen Pharmaceutica), cyproheptadine (from Serva), quipazine (S. Ordzhonikidze All-Union Pharmaceutical Chemical Research Institute, supplied by Professor N. N. Suvorov). The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Data on the time course of avoidance behavior under acute emotional stress, before and after administration of the serotoninergic drugs, are given in Table 1. In agreement with previous observations [1], the first time the untrained animal was placed in a glass cylinder fixed in a vessel of water, so that the only way of avoidance was by diving, the rats developed an emotional stress response, largely because of lack of information on the method of avoidance.

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TABLE 1. Effect of Serotoninergic Drugs on Dynamics of Avoidance Behavior under Acute Stress (M ± m)

Drug	Dose, mg/kg	Interval after injection, min	Latent periods of avoidance, sec	Number of unsuccessful attempts at avoidance
Control			39,5±5,3	4,6±0,7
Physiological saline		30	33,5±5,1	5,4±0,8
		180	(++)16,5±4,3	(++)1,9±0,4
Control			37,0±7,5	3,0±2,8
5-HTP	10	30	(+)15,5±3,3**	1,7±1,7
		180	(++)8,1±1,9	0,0**
Control			45,3±12,5	2,7±1,4
5-HTP	40	40	17,7±4,2*	2,3±0,9*
		180	(+)12,7±3,3	0,0**
Control			39,0±7,5	5,7±2,8
Zimelidine	2,5	40	(++)11,2±2,0**	0,1±0,1**
		180	(++) 9,1±2,1	0,1±0,1**
Control			39,0±11,0	1,9±1,4
Zimelidine	15	30	46,7±11,9	10,6±4,8
		180	(+)13,9±4,8	0,0**
Control			32,5±4,7	2,5±0,9
Trazodone	2,5	30	31,0±4,8	(+)5,2±1,2
		180	(++)11,3±1,7	2,1±0,9
Control			38,6±6,8	4,7±2,1
Trazodone	10	30	(+)10,8±1,3**	(+)0,0**
		180	(+)13,6±1,8	(+)0,0**
Control			37,7±8,3	4,4±1,5
CPP	5	30	62,8±13,5*	2,3±0,7**
		180	59,0±16,3	3,1±1,7
Control			38,8±1,1	2,3±0,7
Quipazine	7	30	(++)88,0±15,9**	(+)11,8±2,8**
		180	37,8±9,9	3,0±2,8
Control			39,2±13,4	9,6±3,5
Pirenpiron	0,02	30	(+)7,0±1,8**	(+)0,6±0,3**
		180	16,8±5,5	3,0±1,6
Control			45,5±18,3	6,5±3,3
Cyproheptadine	0,5	30	12,2±3,3**	0,5±0,5**
		180	(+)4,3±1,7**	0,8±0,3*

Legend. In each experiment n = 6. (+) Denotes $P < 0.05$, (++) $P < 0.01$ (relative to internal control); *$P < 0.05$, **$P < 0.01$ (relative to animals receiving physiological saline).

Violent affective behavioral responses (jumping upward, spinning) interfered with extrapolation of the situation and the making of the only adequate decision which could lead to freedom. Individuals succeeding in achieving avoidance during 2 min of testing were selected for the experiments. On retesting 2-2.5 h after the control test, and 30 and 180 min after injection of physiological saline (control group), the latent period of diving was shortened, and the number of incorrect attempts at avoidance also was reduced. This was due to partial learning by the animal and a fall in the level of affective responses on repetition of the experimental situation.

5-HTP, the 5-HT precursor, led to dose-dependent shortening of the latent period of realization of avoidance behavior and reduced the number of unsuccessful attempts at avoidance. Purposeless affective responses were completely suppressed, especially after injection of 40 mg/kg of 5-HTP. This is in agreement with data [2] on the facilitating effect of 5-HTP on avoidance realization in an aversive situation. Zimelidine, a selective inhibitor of serotonin reuptake [16], in a small dose (2.5 mg/kg) facilitated realization of avoidance behavior. In a large dose (15 mg/kg), however, the number of unsuccessful attempts at avoidance increased after 30 min, as also did the latent period of avoidance. Quipazine, an agonist of postsynaptic serotonin receptors [17], was directly opposite in its effect on avoidance behavior to the other serotoninomimetic drugs (5-HPT, zimelidine in a small dose). Quipazine lengthened the latent period of avoidance and increased the number of unsuccessful attempts to escape, and also raised the level of the animals' affective responses. Trazodone in small doses (2.5 mg/kg), with a predominantly blocking action on postsynaptic serotonin receptors [14], gave no significant effects (compared with the group of rats receiving physiological saline). In a large dose (10 mg/kg) with a mainly serotoninomimetic action [3], trazodone depressed affective hyper-reactivity and shortened the latent period of avoidance behavior considerably. Effects of trazodone developing 20-40 min after its administration are associated with the formation of its active metabolite — CPP [15, 18]. However, the effect of a large dose of trazodone differed from the action of CPP. Despite the fact that the

animals' affective responses also were weakened by CPP, realization of avoidance behavior was impaired (lengthening of latent periods at the 2nd and 3rd tests) and the number of unsuccessful attempts at diving increased. Pirenpiron, a selective blocker of presynaptic S_2 serotonin receptors [12], optimized realization of avoidance behavior: the latent period of diving was sharply reduced and affective manifestations were almost completely suppressed. Since the effect of pirenpiron was brief, the results of testing 180 min after its administration did not differ from the control. Cyproheptadine, with a similar but more prolonged blocking action on serotonin receptors, gave a similar effect.

It can be concluded from analysis of the data that the optimizing action of various serotoninergic drugs on avoidance behavior under stress is largely due to depression of the animals' emotional reactivity, which leads in turn to weakening (suppression) of purposeless "panic" responses. Since the rate of realization of avoidance behavior is inversely proportional to the level of affective responses, this factor facilitates manifestation of extrapolating activity—discovery of the method of avoidance (diving) and consolidation of the skills. 5-HTP acts in this way. Injection of the precursor increases the brain 5-HT concentration within 30 min [20]. Potentiation of synthesis and secretion of the mediator leads to weakening of aggressive-defensive manifestations and locomotor activity [5, 8]. However, deeper sedation and depression of motivational activity under the influence of CPP, chosen as powerful serotonin-positive effects [9], impairs realization of avoidance behavior. The different effects of small and large doses of zimelidine are in agreement with the characteristics of its neurochemical action. In a smaller dose zimelidine selectively inhibits 5-HT reuptake [16]. However, in larger doses, besides inhibition of 5-HT uptake, uptake of noradrenalin (NA) also is inhibited. Under conditions of acute stress, when NA release is intensified [21, 22], thus causing hyper-reactivity and excessive motor activity in the animals, inhibition of NA uptake potentiates its postsynaptic action. The inhibitory effect of zimelidine on avoidance behavior is replaced after 180 min by an activating effect (just as with a small dose). This is due to the rapid transformation of zimelidine *in vivo* into norzimelidine, which has a much more selective action on 5-HT uptake [16] than zimelidine. Zimelidine does not affect learning of the avoidance response in rats but considerably reduces aggressiveness [16]. These pharmacological effects contribute to a reduction of the affective manifestations during stress. Quipazine has not only a serotoninomimetic action, but also a dopaminomimetic action [9], and it also blocks presynaptic inhibitory α-adrenoreceptors [19], leading to intensified release of NA. Quipazine therefore potentiates motor activity and induces affective reactions [17, 18]. Since desynaptic autoreceptors are located both on serotoninergic raphe neurons and on serotonin-containing terminals of the central cortex [7], the blocking of these receptors by pirenpiron and cyproheptadine leads to increased release of 5-HT from the terminals and to quickening of the tonic discharge of neurons of the raphe nuclei. Meanwhile the inhibitory influence of the serotoninergic system on dopaminergic mechanisms is potentiated [13]. Both pirenpiron and cyproheptadine also have a dopamine-blocking effect [12].

It can be concluded from an analysis of these results that drugs which directly or indirectly activate the serotoninergic system (5-HTP, zimelidine in small doses, pirenpiron, cyproheptadine) have a positive effect on goal-directed behavior in an acute stress situation. Drugs with a dopaminomimetic or noradrenalinomimetic action aggravate the negative effect of stress on behavior. A combination of serotonin-blocking (blocking S_2 autoreceptors) and dopamine-blocking (blocking of dopamine receptors) effects, in the case of pirenpiron and cyproheptadine, leads to the optimal result.

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ROLE OF THE HIPPOCAMPAL THETA RHYTHM IN THE MECHANISM OF THE ANXIOLYTIC ACTION OF PHENAZEPAM

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KEY WORDS: benzodiazepines; phenazepam; hippocampal theta rhythm; conflict situation.

Previous investigations into the effect of tranquilizers on behavior of animals in a conflict situation revealed positive correlation between the intensity of their anticonflict action and their anxiolytic action in clinical practice. Correlation also was found between activity of the benzodiazepines under experimental and clinical conditions and the degree of their binding with benzodiazepine receptors [9, 11].

To determine the electrophysiological mechanisms of the anxiolytic action of benzodiazepines, in the investigation described below the effect of the benzodiazepine tranquilizer phenazepam on the functional state of various regions of the brain was studied in rats during the formation of conflict behavior.

EXPERIMENTAL METHOD

Experiments were carried out on 20 male rats weighing 180-200 g with electrodes implanted chronically into the motor cortex, dorsal hippocampus, lateral hypothalamus, and anterior thalamus. Potentials were derived by a monopolar method through implanted nichrome wire electrodes 90 μ in diameter, insulated with varnish. The reference electrode was applied to the nasal bone. Coordinates of insertion of the electrodes were calculated from an atlas of the rat brain [3]. Electrical activity was recorded on a 17-channel Nihon Kohden electroencephalograph from unrestrained animals and the traces were subsequently processed on an MAG-4V automatic integrator.

After deprivation of food and water for 48 h, inducing a motivation to drink, a stable conditioned drinking reflex was established in the rats. A conflict situation was created by collision between drinking and defensive motivation, by applying painful electric shocks to the animal while obtaining water in the customary situation of the drinking reflex [6]. Brain electrical activity was recorded on the days of training: during deprivation of drinking and 5 min after the beginning of drinking, i.e., after satiation. On the experimental days electrical activity was recorded before drinking and again 2-3 min after stimulation of the rat with electric shocks.

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