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5-HT_{1A}-RECEPTOR AGONISTS RESTORE BEHAVIOR OF RATS WHEN DISTURBED BY L-DIHYDROXYPHENYLALANINE

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The serotonin (5-hydroxytryptamine, 5-HT) system of the brain has a regulatory and modulating influence on the dopamine and noradrenalin system [8], which are directly involved in the expression of emotional-behavioral reactivity, sensomotor integration, and attention. An excessive increase in the concentration of exogenous dopamine (DA) and noradrenalin (NA) in the brain after injection of L-dihydroxyphenylalanine (L-dopa) causes a change in emotional reactivity, and disturbs locomotor and investigative activity and also the complex elementary rational behavior in an acute stress situation [2]. On the basis of data on the normalizing effect of the anxiolytic huspirone (which interacts with 5-HT, DA, and NA-neurotransmitter systems) and other 5-HT_{1A} agonists on behavior in stress-conflict situations [3], we studied the degree to which selective and unselective agonists of 5-HT_{1A}-receptors and also indirect 5-HT agonists can influence avoidance behavior in an acute stress situation, when disturbed by L-dopa.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male rats weighing 180-250 g. The animals were first adapted by keeping them for 2 days in the experimental room at 20 ± 2°C, with natural alternation of daylight and darkness, and with free access to water and food. The effect of the substances on ability of the animals to solve an extrapolation problem based on escape from an acute stress situation, disturbed by L-dopa, was studied by the method developed previously [1]. The animals were tested once in the course of 2 min. The latent period (LP) of the motor reactions, the number of unsuccessful attempts to escape, and LP of deliverance were recorded and the percentage of the animals giving the corresponding pattern of behavior was calculated. At least 15 rats were used for testing each dose of the substance. A disturbance of behavior was induced by injecting Madopar in a dose of 125 mg/kg (containing 100 mg of L-dopa and 25 mg of benserazide, an inhibitor of peripheral aromatic amino-acid decarboxylase) 1 h before testing. *p*-Chlorophenylalanine (PCPA) was given over a period of 48 h in a dose of 300 mg/kg. With the exception of L-5-hydroxytryptophan, m-hydroxybenzylhydrazine (NSD-1015), mianserin and yohimbine, which were given 10 min before injection of Madopar, all the other substances were given 20 min before testing. Buspirone, 5-methoxy-N,N-dimethyltryptamine (5-MeODMT), *m*-chlorophenylpiperazine (mCPP), quinazine, 8-hydroxy-2-(di-*n*-propylamino)tetraline (80H-DPAT),

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TABLE 1. Effect of 5-HT Positive Substances on Madopar-Disturbed Avoidance Behavior in an Acute Stress Situation

Substance, mg/kg	LP of motor responses	Number of attempts to escape	LP of escape, sec	% animals with corres. patterns
Physiological saline	10,6	7	24.3	75
Madopar (M), 125+ physiological saline	3*	120**	∞**	92
M+NSD-1015,100	35**	18,5**	71,3**	82
M+L-5-hydroxy-tryptophan, 200	39**	23**	∞	88
M+ cytalopam: 5	8,1*	49,4**	∞**	95
10	11,5*	25,3**	∞	96
M+ M-CPP				
0,15	9,3*	11,10**	33,6**	50
0,25	14,4**	22,2**	49,1**	60
0,35	23	35,3**		80
0,50	35,2	8,4**		80
1	8,6*	0**		100
M+5-MeODMT, 4	34**	4,5**	41,3**	70
M+ buspirone, 4	9,3**	13,4**	47**	70
M+8-OH-DPAT	7*	3,8**	12,5**	75
M+mianserin: 5	5,2	132	∞	100
10	6,3	38,4**	∞	75
20	4	20**	27,4**	50
M+ quipazine:				
1	5	140	∞	80
4	40**	23**	∞	90
M+ cyproheptadine, 1	11*	110	∞	80
M+yohimbine, 2	3,8	120	∞	95
P+ PCPa, 300 + M	3,3	140	∞	100

Legend. Asterisk denotes significant differences between effect of Madopar and control; crosses indicate the same, between effect of substances together with Madopar and effect of Madopar alone. $*p < 0.05$, $**p$, and $++ p < 0.01$.

NSD-1015, mianserin, cytalopram, and yohimbine were dissolved in physiological saline; Madopar, PCPA, cyproheptadine, and L-5-hydroxytryptophan were made up in a 1% suspension of Tween-80. All the substances were injected intraperitoneally. The results were subjected to statistical analysis by the Wilcoxon—Mann—Whitney tests.

EXPERIMENTAL RESULTS

In a situation of acute emotional stress (placing the rats in water inside a cylinder) escaping behavior was observed in only 75% of the intact animals (Table 1). Injection of Madopar caused an increase in emotional-behavioral reactivity. Compared with the control, LP of the motor responses was reduced by 3.5 times, the number of unsuccessful attempts at escaping was increased 17-fold, and 92% of the animals were unable to realize avoidance behavior. Preventing the formation of exogenous DA by preliminary administration of NSD-1015, an inhibitor of the central decarboxylase of aromatic amino acids, abolished the disorganizing effect of Madopar.

Injection of selective (8OH-DPAT) and unselective (buspirone, 5-MeODMT) 5-HT_{1A} agonists caused an effective decrease of emotional and behavioral reactivity in a stress situation, manifested as an increase in LP of the motor reactions and a decrease in the number of unsuccessful attempts to escape. Avoidance behavior was observed under these circumstances in 70-75% of animals. The mechanism of interaction of 5-HT with the catecholamine systems of the brain is still largely unexplained. Loading with L-dopa led to inhibition of the spike discharge of DA-neurons [5]. It was mainly the mesofrontal (by contrast with nigrostriatal and mesolimbic) DA neurons with a high firing rate and a small DA pool [13], facilitating disturbances of higher integrative functions of the brain, that were subjected to this influence to the greatest degree. Buspirone, an agonist of 5-HT_{1A}-receptors, can block the inhibitory effect of iontophoretically applied DA on spike activity of DA neurons in area A-10 [12]. It is suggested that the disinhibitory effect of 5-HT_{1A}-agonists is due to their interaction with postsynaptic 5-HT_{1A}-receptors

located on the bodies and dendrites of DA-neurons in the midbrain [7], which abolishes the inhibitory effect of L-dopa on the regulatory function of the neocortex.

Quipazine, an unselective agonist of 5-$HT_{1,2,3}$-receptors, had no normalizing effect. However, the unselected nonindole agonist of 5-HT_1- and 5-HT_2-receptors, m-CPP, in low doses (0.15, 0.25 mg/kg), and also the 5-HT_2-blocker mianserin, in a high dose (20 mg/kg), but not cyproheptadine, abolished the disorganizing effect of Madopar in only 50-60% of animals. Buspirone and m-CPP have high affinity for α_2-adrenoreceptors and also possess a yohimbine-like effect to some degree [9]. However, administration of the α_2-antagonist yohimbine had no effect on behavior of rats when disturbed by Madopar. Evidently, α_2-adrenoblocking activity for buspirone and m-CPP and 5-HT_2-blocking activity for mianserin are not decisive relative to the normalizing effect. The effect of large doses of mianserin have been shown to be similar to that of the classical neuroleptics, whereas m-CPP can release 5-HT from terminals of 5-HT-neurons [11].

5-HT is a nonspecific agonist of 5-HT-receptors, and a change in its concentration in the brain has a marked psychotropic action. However, inhibition of tryptophan hydroxylase activity following administration of p-CPA led to a change in the effect of Madopar. Conversely, administration of the 5-HT precursor L-5-hydroxytryptophan, the 5-HT reuptake inhibitor cytalopram, quipazine, and high doses of m-CPP caused a marked reduction in the number of unsuccessful attempts at avoidance and, due to immobility, an increase in LP of the motor responses. However, these changes did not facilitate the appearance of avoidance behavior. The results are in agreement with data on weakening of locomotor and defensive reactions, arising in response to intensification of 5-HT synthesis and release [6]. Nevertheless, potentiation of 5-HT activity, induced by injection of indirect 5-HT agonists, is not sufficient to restore normal avoidance behavior when disturbed by Madopar.

It is thus mainly 5-HT_{1A}-receptor agonists that can restore avoidance behavior, disturbed by L-dopa, in an acute stress situation. It can be tentatively suggested that this phenomenon is based on the ability of L-dopa to selectively enhance the sensitivity of 5-HT_{1A}-receptors, which is preferable for manifestation of the effects of the corresponding agonists. In animals with unilaterally supersensitive 5-HT-receptors of the substantia nigra agonists of 5-HT_{1A}-receptors are more effective at inducing rotational behavior than agonists of other subtypes of 5-HT_1-receptors [4]. During L-dopa loading, an acute increase in the sensitivity of mesencephalic postsynaptic 5-HT_{1A}-receptors may arise as the result of exhaustion of 5-HT, caused by DA, for if its concentration is high, release of 5-HT from its depots is observed [10].

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