ETHOPHARMACOLOGICAL ANALYSIS OF THE EFFECTS OF THYROLIBERIN AND MELANOSTATIN ON A MODEL OF TIMID DEFENSIVE BEHAVIOR IN MICE

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It was shown previously that the neuropeptides thyroliberin (thyrotropin releasing hormone, TRH) and melanostatin (melanotropin potentiating factor, MPF) potentiate the aggressive behavior of isolated mice and modify their intraspecific behavior [3, 7]. These effects of tripeptides have been shown to be mediated partially by dopaminergic, GABA-ergic, and opiate mechanisms. However, the effect of these peptides on timid-defensive behavior, arising in animals during stress of intraspecific confrontation, remains totally uninvestigated. It is possible that victories or defeats in intraspecific conflicts may lead to lasting neurochemical changes in the brain, as is confirmed by the different sensitivity of aggressive and submissive animals to neuropharmacological agents [3, 4, 8].

The aim of this investigation was a neuropharmacological and ethological analysis of the action of TRH and MPF-I on the behavior of mice with a timid-defensive type of behavior and, in particular, to analyze the role of dopaminergic and GABA-ergic systems in the realization of the action of peptides on intraspecific behavior.

EXPERIMENTAL METHOD

Experiments were carried out on 84 male CC57W albino mice weighing 22-30 g, kept in isolation. For 5 min daily for 2 weeks the mice were subjected to painful electrical stimulation of threshold strengths applied through the electrode floor (bursts of square pulses with a strength of 2 mA and following frequency of 1 Hz) and they were also made to share a cage with aggressive males, the number of attacks by which was limited to 10. As a result the mice developed a timid-defensive behavioral profile. The behavior of these animals was tested with a nonaggressive partner, kept in a group for 4 min. Behavioral units were recorded and subjected to primary analysis by means of a computerized ethograph, based on the Élektronika DZ-28 display microcomputer [3, 7]. TRH and MPF-I were injected in a dose of 10 mg/kg 5 and 20 min beforehand. Together with the neuropharmacological agents (in a dose of 0.5 mg/kg) the peptides were injected 5 min before testing, muscimol 30 min before, and bicuculline, apomorphine, and haloperidol 15 min before testing. All substances were injected intraperitoneally. The significance of differences (control — experiment) was determined by Wilcoxon's nonparametric test for paired and independent samples.

EXPERIMENTAL RESULTS

TRH induced characteristic changes of individual behavior in the mice in the form of activation of locomotion and self-grooming; locomotion increased, moreover, on account of the duration of the action and not an increase in their frequency (Tables 1 and 2). Meanwhile a deficiency of intraspecific contacts between the animals (sociability) was observed. Under the influence of TRH the relations between the defensive postures changed: the total duration of the sideways defensive postures increased, whereas that of the vertical defensive postures decreased. Although these changes did not reach the level of significance, they were systematic in character and they were also found when neuropharmacological agents were used. The behavioral profile as a whole returned to its initial state 20 min after injection of TRH,

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TABLE 1. Changes in Frequency of Behavioral Actions of Mice under the Influence of TRH and MPF-I and Their Combinations with GABA- and Dopaminergic Drugs (in % of control)

Substances	Individual behavior				Intraspecific behavior	
	static postures	locomotion	self-grooming	vertical activity	defensive behavior	sociability
TRH (after 5 min)	+12	+25	+1100*	—18	—31	—70*
TRH (after 20 min)	+11	+14	+100	—21	—7	—52*
MPF-I (after 5 min)	—14	—6	+500	—2	—19	—33
MPF-I (after 20 min)	+2	+7	+100	—21	—46	—6
Muscimol	—23	—4	+100	—66*	—31	—52*
TRH + muscimol	+12	—29*	0*	—98*	—2	—81*
MPF-I + muscimol	—15	—36	+100	—81*	+21	—98*
Bicuculline	+1	+17	+600	—54*	+21	—23
TRH + bicuculline	+7	+32*	+1100*	—77*	+25	—73*
MPF-I + bicuculline	+11	+4	+1200*	—52*	+25	—60*
Apomorphine	+8	+54*	+900	—18	—17	—68*
TRH + apomorphine	—8	—24*	+2100*	—74*	—29*	—96*
MPF-I + apomorphine	+18	+48*	+100	—18	—2	—75*
Haloperidol	—32	—48*	+700*	—86*	—68*	—81*
TRH + haloperidol	—57*	—70*	+700*	—98*	—73*	—97*
MPF-I + haloperidol	—16	—33*	+900	—60*	—38*	—87*

Legend. Here and in Table 2: *) Differences significant compared with control ($p < 0.05$). A (+) or (—) sign before the numbers shows the direction of the effect.

TABLE 2. Changes in Duration of Behavioral Actions of Mice under the Influence of TRH and MPF-I and Their Combinations with GABA- and Dopaminergic Drugs (in % of Control)

Substances	Individual behavior				Intraspecific behavior	
	static postures	locomotion	self-grooming	vertical activity	defensive behavior	sociability
TRH (after 5 min)	+81*	+50*	+504*	—38	—16	—79*
TRH (after 20 min)	+28	+23	—69	—38	+17	—46*
MPF-I (after 5 min)	+2	+7	+25	+14	+89	—46*
MPF-I (after 20 min)	+54	—3	—69	—14	—25	—5
Bicuculline	+20	+29*	+77	—62*	+116*	—31
TRH + bicuculline	+25	+61	+650*	—86*	+95	—27
MPF-I + bicuculline	+33	+39*	+806*	—47	+115*	—79*
Muscimol	+118*	+4	+171	—87*	+38	—73*
TRH + muscimol	+163*	+8	—100*	—99*	+73	—47*
MPF-I + muscimol	+39	—21	+4	—84*	+228*	—71*
Apomorphine	+60*	+90*	+192*	—37	—13	—83*
TRH + apomorphine	+108*	+92*	+442	—77*	—19	—97*
MPF-I + apomorphine	+77*	+31*	—69*	—23	+33	—84*
Haloperidol	+144*	—55*	+806*	—83*	+92	—91*
TRH + haloperidol	+195*	—70*	+369*	—98*	+9	—99*
MPF-I + haloperidol	+155*	—29*	+493	—51	+60	—91*

and only intraspecific sociability remained depressed. MPF-I caused no significant change in individual behavior, it activated self-grooming, reduced intraspecific sociability, and increased the duration of defensive behavior (Table 2).

Injection of the GABA antagonist bicuculline together with the peptides led to an increase in duration of the defensive postures, locomotion, and self grooming. Bicuculline aggravated the deficiency of intraspecific sociability arising as a result of MPF-I. Injection of the GABA agonist muscimol reduced the stimulating action of TRH on locomotor activity and potentiated its inhibitory effect on intraspecific sociability. Muscimol together with TRH and MPF-I increased the frequency and duration of defensive behavior.

Apomorphine, an agonist of dopamine receptors, sharply reduced intraspecific sociability and potentiated various forms of individual behavior (Tables 1 and 2). The frequency and duration of defensive actions and postures were not significantly changed under these circumstances. Injection of TRH potentiated the basic effects of apomorphine except its effect on locomotion. TRH increased the duration of static postures and aggravated the deficiency of sociability caused by haloperidol, an antagonist of dopamine receptor systems. TRH counteracted the activating effect of haloperidol on defensive behavior (especially on the duration of the action; Table 2). Injection of MPF-I led to reduction of the inhibitory action of haloperidol on locomotor activity and its activating effect on defensive behavior.

It can be concluded from these data that the quality of the psychotropic effects of TRH and MPF-I is determined by the initial individual-typologic characteristics and the dominant behavior profile, determined by differences of intraspecific experience acquired in a situation of intraspecific confrontation, as other experiments also have confirmed [2, 3, 6, 7]. Since oligopeptides have recently come to be regarded as modulators of mediator processes [1, 5], the differences which exist between the action of the peptides on timid-defensive (the data published in this paper) and aggressive [3, 7] behavior may be linked with reorganization of the function of mediator systems (including GABA-ergic and dopaminergic), and in the number and affinity of the specific binding sites of the neurotransmitters. TRH and MPF-I can themselves potentiate timid-defensive behavior and reduce intraspecific sociability in isolated mice. GABA deficiency can potentiate timid behavior, whereas potentiation of GABA-positive influences is related more closely to depression of the activating effects of oligopeptides on individual activity. TRH and MPF-I counteracted the potentiation of defensive behavior due to the action of the dopaminolytic haloperidol. It can be postulated that TRH and MPF-I have the property of mobilizing agonistic behavior, and that this property includes an anxiogenic component, which may be realized as the potentiation of both timid-defensive and aggressive behavior [3].

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