THE PSYCHOPHARMACOLOGICAL SPECTRUM OF MELANOSTATIN

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Melanostatin, a hypothalamic factor inhibiting the release of the melanocyte-stimulating hormone of the anterior pituitary, has been isolated and identified as the tripeptide L-prolyl-L-leucylglycinamide. This same group is the C-terminal tripeptide of oxytocin, with the amino acid sequence 7-9 [11]. It potentiates the behavioral effects of L-dopa and 5-hydroxytryptophan and antagonizes oxotremorine tremor in both intact and hypophysectomized animals, which indicates that melanostatin acts directly on the brain. On the basis of data indicating its dopamine-potentiating action, melanostatin has been used for the treatment of Parkinsonism in man [8, 10]. However, there is some evidence [5] that this effect of melanostatin differs from that of typical stimulators of dopamine receptors [7].

The object of this investigation was to make a more detailed study of the spectrum of psychotropic action of melanostatin (synthesized at the Experimental Factory, Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, by Candidate of Chemical Sciences A. P. Pavars) and the possible neurochemical mechanisms of its action.

EXPERIMENTAL METHOD

The spectrum of emotional-behavioral reactivity was assessed in cats (six animals) under group-interaction conditions by the method developed previously [1]. The semantic content of the response manifestations was assessed qualitatively and quantitatively (on a five-point system) on the basis of evaluation tables [4]. The response of self-stimulation of the brain was assessed on rats with electrodes implanted into the region of the substantia nigra. Pedal self-stimulation with fixed duration (0.25 sec) of the volley of pulses (100 Hz, 1 msec, 300 μA) was carried out. The concentrations of dopamine (DA) and its metabolite, homovanillic acid (HVA), of noradrenalin (NA), serotonin (5-HT) and of its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), was determined in the rats' brain spectrofluorometrically. Effects on haloperidol catalepsy were determined after 10, 30, 60, and 120 min by counting the number of animals in a cataleptic state for over 2 min. The antireserpine action was assessed by changes in the rectal temperature 15, 30, 60, 120, 180, 240, and 300 min after injection of the preparation into previously reserpinized albino mice.

EXPERIMENTAL RESULTS

In the original spectrum of emotional-behavioral reactivity of the cats, 15-30 min after its administration melanostatin (20-40 mg/kg, intraperitoneally) narrowed the spectrum of emotionally positive behavioral manifestations (complete abolition of expression of satisfaction, curiosity, or play) and reduced investigative activity in relation to new objects or territories. Manifestations of aggressiveness, especially in response to provocation, and of active-defensive behavior in response to aversive tests increased. Interdependent behavior with partners became more conflicting: episodes of fighting increased in severity and duration. Predatory manifestations of hunting for mice were intensified, with rapid killing of the victim without any preliminary play ritual. Spontaneous movements and initiativeness of behavior were diminished (Fig. 1).

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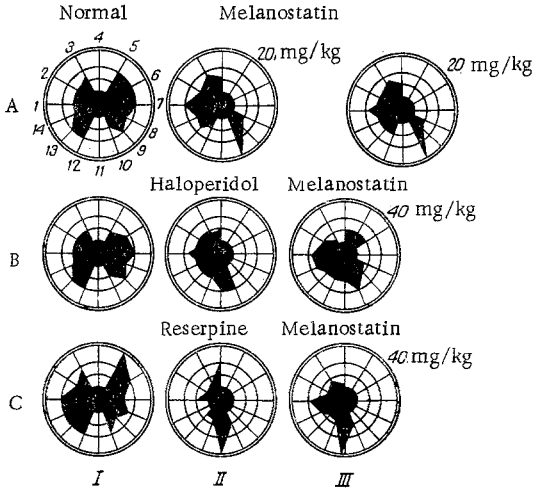

Fig. 1. Changes in spectrum of emotional reactivity in cats under the influence of melanostatin. A, B, C) Spectra of emotional reactivity of animals. I) Before administration. A: (II, III) After single and repeated doses of melanostatin, 20 mg/kg, respectively. B and C: II) After administration of haloperidol and reserpine, respectively; III) after two injections of melanostatin in a total dose of 40 mg/kg. 1-14) Components of spectrum of emotional reactivity: 1) rage, 2) fear, 3) anxiety, 4) negativity, 5) curiosity, 6) satisfaction, 7) play, 8) hunting, 9) kindness, 10) confliction, 11) inadequacy of behavior, 12) initiative, 13) motor activity, 14) orienting activity.

Changes in the spectrum of emotional reactivity arising under the influence of melanostatin did not differ in their behavioral manifestations from those following injection of L-dopa and amantadine (midantan) [2]. All three compounds are characterized by the "explosiveness" of behavior (intensification of the affective and conflictive sides of behavior accompanied by motor inhibition), activation of emotionally negative manifestations, together with reduction of behavioral manifestations of emotionally positive responses. According to the observations of Pelletier et al. [12], melanostatin in cats in doses of 10-50 mg/kg does not affect stereotyped behavior evoked by L-dopa, but inhibits the increase in motor activity induced by L-dopa.

The brain self-stimulation reaction in rats, reflecting the functional state of the positively reinforcing systems of the brain [3], showed a tendency toward slight inhibition under the influence of melanostatin. The mean values of this test ($\bar{x}$, $n = 5$) for observations lasting 5 min (30 min after injection of the substance) were as follows: after melanostatin in a dose of 15 mg/kg 290.2, in a dose of 20 mg/kg 297.0, compared with a normal level of 307.4.

In reserpinized mice (5 mg/kg, intraperitoneally, 24 h beforehand) melanostatin (5 mg/kg, intraperitoneally) antagonized reserpine hypothermia. After 15 min the rectal temperature increased by 2 ± 0.5°C. The effect increased with an increase in time (3.1 ± 0.8°C after 30 min, 4 ± 0.7°C after 60 min), reached a maximum (4.7 ± 0.5°C) after 120 min, and persisted for 3-4 h. With effect from the first few minutes after injection of melanostatin the muscle tone of the animals increased and their ptosis decreased by 20-30%. These effects continued for 2-3 h. Deep reserpine depression (0.25 mg/kg intramuscularly, twice a day for 2 days) in cats is manifested by marked hypodynamia, a characteristic posture of "cateplexy" (the limbs crossed, the head lowered to the ground, the tail thrown to one side, the ears wide apart and still), by vocal responses, and by a disturbance of the adequacy of response. To provocation the animal emerged from its state of "cataplexy" and exhibited active protective-defensive behavior, with vocal responses of threatening character and hyperreflexia. A single injection of melanostatin (20 mg/kg) had no significant effect on the depressive state, but significantly increased (by 0.8-2.4°C) the rectal temperature, when depressed by reserpine, for more than 1 h. After two injections of the substance in the course of 24 h in a total dose of 40 mg/kg, active-defensive

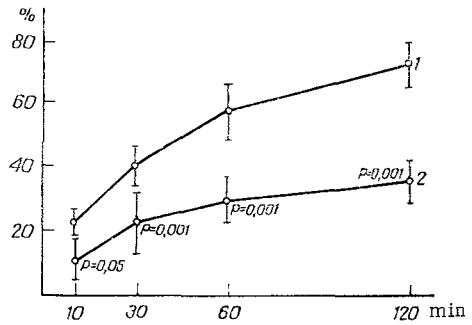

Fig. 2. Anticataleptic activity of melanostatin (5 mg/kg, intraperitoneally) in albino mice after injection of haloperidol. 1) Control (haloperidol 5 mg/kg); 2) injection of melanostatin 15 min before haloperidol. Abscissa, time (in min); ordinate, number of mice in state of catalepsy (in % of whole group of animals).

TABLE 1. Effect of Melanostatin on Content (in %) of Biogenic Amines in Brain Compared with Control (sterile bidistilled water)

Group of animals	Series	Concentration of monoamines (M ± m)				
		NA	DA	HVA	5-HT	5-HIAA
Intact mice	Control	100±12	100±7	100±15	100±17	100±20
	Melanostatin	101±7	102±5	95±9	101±9	110±5
Reserpinized mice	Control	60±10	40±4	60±7	50±5	60±10
	Melanostatin	67±5	43±7	83±9*	55±15	61±10
Mice receiving haloperidol	Control	90±15	50±5	500±10	95±13	99±10
	Melanostatin	95±8	50±7	400±5*	95±10	100±10
Rats (intraventricular injection of 100 μg melanostatin)	Control	100±18	100±10	100±16	100±10	100±12
	Melanostatin	110±13	153±13*	135±8*	90±7	95±12

*$P \leq 0.05$ relative to control in each group of animals.

behavior in response to provocative actions of minimal intensity was activated somewhat, though without restoration of emotionally positive responses.

Melanostatin (5 mg/kg, intraperitoneally), if injected 15 min before haloperidol (5 mg/kg) reduced the percentage of mice with manifestations of catalepsy compared with the control (Fig. 2). In cats with experimental haloperidol depression (1 mg/kg intraperitoneally twice a day for 4 days), the characteristic posture of "cataplexy" accompanied by constant vocal responses, hypodynamia, and catalepsy (maintenance of an uncomfortable posture on a stand for up to 5 min), melanostatin (20 mg/kg) had a definite activating effect. The animal more easily emerged from the state of cataplexy, goal-directed investigative behavior was observed, orienting reactions to contact-making stimuli were strengthened, motor activity was increased, and the spectrum of emotional-behavioral reactivity was somewhat widened.

Determination of the brain myogenic amine levels in rats (Table 1) showed that melanostatin increases the content of HVA, a metabolite of DA, when reduced by reserpine, and reverses the increase in HVA induced by haloperidol. Intraventricular injection of melanostatin (1 μg) into rats increased their motor activity, induced shakes of the head and of the wet dog type, sneezing, and grooming. The animals were decapitated at the height of the behavioral manifestations (after 20 min). An increase in the content of DA and its metabolite, HVA, was found in the brain. This is evidence of increased synthesis of DA and of its more rapid turnover.

Melanostatin thus influences dopaminergic processes when inhibited by reserpine and haloperidol. With no antidepressive effect of its own, in the case of reserpine depression melanostatin activates aggressive-

defensive behavior somewhat (i.e., exhibits an action similar to that of other dopaminomimetic agents such as L-dopa and amantadine), and in experimental haloperidol depression it weakens aggressive behavior induced by provocation, and widens the spectrum of emotional reactivity. To determine the more precise neurochemical mechanism of melanostatin, further analysis is required. Although it potentiates behavior manifestations evoked by apomorphine, melanostatin itself does not induce amphetamine stereotype in rats [7]. Data showing an increase in the intensity of synthesis and turnover of DA in the striatum and caudate nucleus [15] do not agree with the negative results of other experiments [9, 14]. The effect of melanostatin on monoamine metabolism is not the same in different brain structures. Selective binding of melanostatin in neurons has been demonstrated by autoradiography [13], so that the presence of specific receptors may be postulated. Melanostatin exhibits an anticataleptogenic effect after administration both of neuroleptics and of morphine, evidence of its activating effect on DA-mechanisms not only in the striatum, but also in the mesolimbic system [6].

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