modify dopamine release [10]. We likewise were unable to demonstrate any inhibitory effect of enkephalins on GABA release, discovered previously on synaptosomes of whole rat brain [4], possibly due to the absence of GABA-ergic nerve endings sensitive to these peptides in the striatum. It is interesting to compare the absence of effect of DTGE on dopamine release in the presence of a higher concentration of the peptide (10^{-4} M) with the decrease in cataleptogenic activity of DTGE when its dose is increased above the optimal level [2]. It can be tentatively suggested that DTGE, like neuroleptics, has a cataleptogenic action and modulates dopaminergic transmission in the striatum. Dependence of the effect of DTGE on dopamine liberation on its concentration revealed by these experiments could serve as one explanation for the abnormal dependence of the behavioral effect of this peptide on its dose.

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DISSIMILAR EFFECTS OF METHIOTHEPIN AND PIRENPERONE ON BEHAVIORAL EFFECTS OF APOMORPHINE

É. É. Vasar and L. Kh. Allikmets

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KEY WORDS: apomorphine; stereotyped behavior; aggressiveness; serotonin receptors; methiothepin; pirenperone.

There is evidence in the literature that a change in activity of serotoninergic processes leads to dissimilar changes in the behavioral effects of apomorphine. Small doses of serotoninomimetics appreciably potentiate apomorphine stereotypy, but destruction of serotoninergic neurons or blockade of serotonin receptors reduces the intensity of stereotyped behavior [4, 6]. Serotonin antagonists and agonists have opposite effects of apomorphine aggressiveness compared with stereotyped behavior. Serotonin antagonists potentiate, whereas agonists inhibit aggressive behavior [7].

It is shown in this paper that on prolonged administration of apomorphine the sensitivity of serotonin receptors linked with aggressive behavior is increased whereas the sensitivity of other receptors, linked with stereotyped behavior, is depressed.

EXPERIMENTAL METHOD

Behavioral experiments were carried out on 150 male Wistar rats weighing 270-320 g. The animals were divided into groups, with 10 to 12 rats in each group. Apomorphine was injected subcutaneously in a dose of 0.5 mg/kg twice a day for ten days. Serotonin antagonists pirenperone (from Jansen Pharmaceutica, Belgium) in doses of 0.07 to 0.3 mg/kg and methiothepin

Departments of Physiology and Pharmacology, Tartu University.

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TABLE 1. Effect of Prolonged Combined Administration of Pirenperone (0.07-0.3 mg/kg) and Methiothepin (0.05-1.25 mg/kg) with Apomorphine (0.5 mg/kg) on Intensity of Apomorphine Stereotypy and Aggressiveness (in Points, M ± m)

Experimental conditions	First day		Third day		Seventh day		Tenth day	
	stereotypy	aggressiveness	stereotypy	aggressiveness	stereotypy	aggressiveness	stereotypy	aggressiveness
Apomorphine (0.5 mg/kg) + physiological saline	3,1±0,18	0	2,7±0,18	0,3±0,22	2,2±0,19	2,3±0,18	2,0±0,17	3,2±0,22
Apomorphine (0.5 mg/kg) + pirenperone (0.07 mg/kg)	2,8±0,21	0	2,6±0,23	2,9±0,25*	—	—	—	—
Apomorphine (0.5 mg/kg) + pirenperone (0.15 mg/kg)	2,7±0,26	0	2,5±0,18	0	2,3±0,22	0,8±0,42*	2,2±0,24	1,0±0.45*
Apomorphine (0.5 mg/kg) + pirenperone (0.3 mg/kg)	2,4±0,34	0	2,4±0,22	0	2,2±0,17	0,3±0,22*	1,7±0,19	0,3±0,22*
Apomorphine (0.5 mg/kg) + methiothepin (0.05 mg/kg)	2,8±0,23	0	2,7±0,29	0	2,4±0,18	3,2±0,19*	—	—
Apomorphine (0.5 mg/kg) + methiothepin (0.25 mg/kg)	2,2±0,17*	0	2,1±0,18	0	1,6±0,14	0*	1,1±0,18*	1,0±0,45*
Apomorphine (0.5 mg/kg) + methiothepin (1.25 mg/kg)	1,7±0,15*	0	1,0±0,12*	0	0*	0*	0*	0*

*P < 0.05 compared with control (apomorphine + physiological saline)

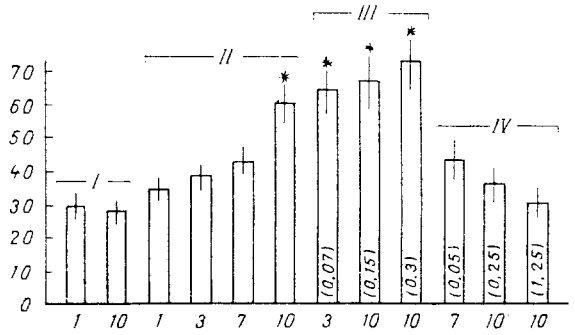

Fig. 1. Head twitches induced by quipazine (2.5 mg/kg) after stopping long-term combined injection of apomorphine with either pirenperone (0.07, 0.15, and 0.3 mg/kg) or methiothepin (0.05, 0.25, and 1.25 mg/kg). Ordinate, number of head twitches. Numbers below columns indicate day of ending administration of apomorphine and serotonin antagonists. I) control, II) apomorphine, III) pirenperone + apomorphine, IV) methiothepin + apomorphine. *P < 0.05 compared with control (physiological saline).

(from Spofa, Czechoslovakia) in doses of 0.05 to 1.25 mg/kg, were injected 30 min before the apomorphine. The behavioral effects of apomorphine were determined on the 1st, 3rd, 7th, and 10th days of injection. The intensity of stereotyped behavior was assessed 15-20 min after injection of apomorphine by the method in [6]. The method suggested by allikmets et al. [3] was used to assess aggressive behavior 25-30 min after injection of apomorphine. If the aggressive responses reached maximal intensity, injection of apomorphine and serotonin antagonist was stopped, and 48 h after the final injection of apomorphine (0.5 mg/kg) the action of quipazine (from Miles Laboratories, England) was studied. Quipazine, an agonist of serotonin receptors with hallucinogenic properties [9], was injected in a dose of 2.5 mg/kg which, as the results of preliminary experiments showed, caused moderate head twitching in all the animals. All the results of the behavioral investigations were subjected to statistical analysis by Dunnett's t test.

EXPERIMENTAL RESULTS

During prolonged administration of apomorphine the intensity of stereotyped behavior gradually weakened (Table 1). There was a parallel increase in aggressiveness, which reached maximal intensity by the 10th day of apomorphine injection (0.5 mg/kg). The aggressive reactions became very violent and fights between the animals often ended with considerable injuries. After discontinuation of the 10-day administration of apomorphine a significant increase in the number of head twitches caused by quipazine in a dose of 2.5 mg/kg was observed (Fig. 1). A small dose of pirenperone (0.07 mg/kg) sharply potentiated the development of apomorphine aggressiveness; the peak exhibition of aggressiveness occurred by the 3rd day of combined injection of apomorphine and a small dose of pirenperone. After stopping this combination considerable potentiation of head twitching was observed after injection of quipazine (Fig. 1) compared with the behavior of animals receiving apomorphine alone. Larger doses of pirenperone (0.15 and 0.3 mg/kg) selectively counteracted the development of apomorphine aggressiveness, whereas the intensity of stereotyped behavior showed no significant change (Table 1). However, these doses of pirenperone not only did not prevent the development of increased sensitivity to the effects of quipazine but, on the contrary, they actually potentiated it. After stopping administration of large doses of pirenperone, the first injection of apomorphine (0.5 mg/kg) induced aggressiveness in all the animals. The antiaggressive action of methiothepin, another antagonist of serotonin receptors, correlated with its antistereotyped action. A small dose of methiothepin (0.05 mg/kg) accelerated the development of apomorphine aggressiveness a little, but not so substantially as pirenperone. Large doses of methiothepin, parallel with inhibition of aggressive behavior, induced a gradual decrease in the intensity of stereotyped behavior (Table 1). When methiothepin was given in a dose of 1.25 mg/kg stereotyped behavior was completely absent on the 7th day of prolonged administration. After stopping combined administration of all doses of methiothepin with apomorphine, the action of quipazine (Fig. 1) was indistinguishable from the results for the control groups. After stopping large doses of methiothepin, injection of apomorphine caused aggressiveness only in some of the animals receiving 0.25 mg/kg of methiothepin.

The results of the experiments with serotonin antagonists are evidence that during long-term administration of apomorphine only the sensitivity of dopamine and also of serotonin receptors remains unchanged. An increase in sensitivity was observed in some serotonin receptors whereas as in others it gradually decreased. The sensitivity of the serotonin receptors connected with the action of pirenperone, a selective antagonist of lysergic acid diethylamide [5], and of hallucinogenic serotoninomimetics was increased. The development of hypersensitivity of these receptors correlates well with a sharp increase in apomorphine aggressiveness. Unlike pirenperone, methiothepin inhibits the development of apomorphine aggressiveness only in doses appreciably depressing stereotyped behavior. Potentiation of the antistereotyped action of methiothepin on prolonged administration is evidence of a gradual decrease in the sensitivity of these serotonin receptors under the influence of apomorphine. Although there is evidence that methiothepin displaces haloperidol and spiroperidol from their binding sites in the frontal cortex [8], our previous investigations showed that the antistereotyped action of dopamine blockers, by contrast with methiothepin, is depressed by combined administration with apomorphine [1, 2].

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