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BRIEF COMMUNICATION

Influence of β-Casomorphins on Apomorphine-Induced Hyperlocomotion

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RÜTHRICH, H.-L., G. GRECKSCH AND H. MATTHIES. *Influence of β-casomorphins on apomorphine-induced hyperlocomotion.* PHARMACOL BIOCHEM BEHAV 44(1) 227–231, 1993. – Derivatives of β-casomorphin Tyr-Pro-Phe-Pro-Gly and their des-Tyr[1]-derivatives were investigated on the model of apomorphine-induced hyperlocomotion (1 mg/kg = 3 μM/kg, IP). D-Pip[4] CM 5 (5 nM) inhibited the apomorphine hypermotility completely, while D-Phe[3] CM 5 (5 nM) and D-Pro[4] CM 5 (5 nM) decreased it only to about 50%. The normal exploration was nearly completely inhibited by D-Pro[4] CM 5 (40 nM), by D-Pip[4] CM 5 (5 nM) depressed to 20%, and by D-Phe[3] CM 5 (10 nM) to 35%. The maximum inhibition of apomorphine-induced hyperlocomotion by the des-Tyr-casomorphin derivatives was about 50%. The dose-response curves were U-shaped. The exploratory activity was not significantly influenced. The mode of action and the involvement of different neurotransmitter systems in the inhibitory effect of β-casomorphin derivatives on apomorphine hyperlocomotion are discussed.

β-Casomorphins Hyperlocomotion Rat Dopamine

MOTOR reactions are in general regarded as the most characteristic behavioral manifestations of stimulation of dopamine receptors. It is well known that stereotypies and hyperlocomotion induced by the dopaminergic agonist apomorphine are mediated by stimulation of postsynaptic dopamine receptors (5,9–11). Even indirectly acting dopaminergic drugs like *d*-amphetamine, cocaine, L-dopa, and others (6,13,18,24) can induce hyperlocomotion. On the contrary, the locomotor activity decreases by inhibition of the dopaminergic system. This can be realized by receptor blockers (2,17,36) after lesion induced by bilateral injections of 6-hydroxydopamine (6-OHDA) (16) or by application of drugs like reserpine or α-methyl-*p*-tyrosine that deplete catecholamines. On the other side, the different sensitivity of the various dopamine receptor subtypes plays an important role in the control of locomotion. Therefore, small doses of dopaminergic drugs like apomorphine or bromocryptine primarily activating the more sensitive presynaptic autoreceptors decrease the dopaminergic transmission, thus lowering locomotor activity (7,33,35).

In this way, the dopaminergic control of motility can be specifically influenced. A direct influence as well as interactions between the different transmitter systems are conceivable.

The β-casomorphin sequences of bovine milk β-casein, which show an opiate-like effect (12,20,21), indicate an effect on the central dopaminergic systems, too (15,19,30). Derivatives of β-casomorphin Tyr-Pro-Phe-Pro-Gly and their des-Tyr[1] derivatives were investigated on the model of apomorphine-induced hyperlocomotion.

METHOD

Animals

Experiments were performed using 8-week-old male Wistar rats from our own breeding stock. Rats were housed in groups of 10 in plastic cages, provided with food and water ad lib, and exposed to a 12 L : 12 D cycle. To arrange for ICV application, a hole (lat. 1.6 mm, AP 0.25 mm) was drilled under hexobarbital/urethane anesthesia through the skull 3 days before the experiment.

Behavioral Observation

The locomotor activity of animals was registered using a self-constructed optoelectric activity meter. Rats were placed on a plate (28 × 45 cm) for 20 min and the horizontal activity was automatically registered by 16 optoelectric cells in the bottom. The motility during exploration was analyzed in the

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TABLE 1
SEQUENCES OF CASOMORPHIN DERIVATIVES AND USED DOSES

Sequence	Shortcut	Dose (nM)
Tyr-Pro-D-Phe-Pro-Gly	D-Phe^{3}CM 5	1, 5, 10
Pro-Phe-D-Pro-Gly	des-Tyr-D-Phe^{3}CM 5	2, 5, 10, 20
Tyr-Pro-Phe-D-Pro-Gly	D-Pro^{4}CM 5	0.1, 0.25, 0.5, 5, 10, 40
Pro-Phe-D-Pro-Gly	des-Tyr-D-Pro^{4}CM 5	0.1, 1, 5, 40
Tyr-Pro-Phe-D-Pip-Gly	D-Pip^{4}CM 5	1, 2, 5
Pro-Phe-D-Pip-Gly	des-Tyr-D-Pip^{4}CM 5	0.1, 0.5, 2, 10

Pip, pipecolic acid.

first 5 min after putting animals into the apparatus and from the 6th to the 20th minute in 5-min intervals. Hyperlocomotion was induced by IP injections of 1 mg/kg (3 μM/kg) apomorphine (Woelm Pharma GmBh, Eschwege, Germany) and we investigated the influence of different drugs on this hyperlocomotion. Control animals received physiological saline IP, respectively.

Drugs and Administration

All drugs were dissolved in or diluted with physiological saline.

Experiment 1. Five minutes after application of 1 mg/kg apomorphine or physiological saline, rats received IP injections of haloperidol (Ratiopharm GmBH & Co., Ulm, Germany) dosed at 0.001 mg/kg (2.7 nM), 0.004 mg/kg (10.8 nM), 0.02 mg/kg (54 nM), 0.1 mg/kg (270 nM), and 1.0 mg/kg (2,700 nM). Immediately after these second injections, rats were put into the apparatus. Control animals received apomorphine and saline IP.

Experiment 2. Five minutes after application of 1 mg/kg apomorphine or saline IP, animals were intracerebroventricularly injected with different β-casomorphin peptides (Table 1) or physiological saline, and put into the apparatus.

For each experiment investigating one dose of one substance, four different treatment groups were used:

1. saline IP + saline ICV
2. apomorphine IP + saline ICV
3. saline IP + haloperidol IP or β-casomorphin derivative ICV
4. apomorphine IP + haloperidole IP or β-casomorphine derivative ICV.

(Per group, 10–15 animals were used, that is, 40–60 animals for each experiment.) All results are statistically evaluated using the Kruskal-Wallis *H*-test followed by the two-tailed Mann-Whitney *U*-test.

RESULTS

The rat motility in the activity meter during the first 5 min was observed as exploratory activity and the activity counts of the saline-saline-injected animals served as the basis for evaluation of results (=100%) (Fig. 1). Such saline control rats showed a mean activity of 119 counts/5 min. The motility from the 6th to the 20th minute was in general considered as locomotor activity. In this case, the apomorphine-induced hypermotility (compared to saline controls) was taken as 100% (Fig. 2). Apomorphine in a dose of 1 mg/kg IP induced in rats about 514 counts/6–20 min. Saline-treated controls showed only an activity of 83 counts during this time. In a preliminary experiment, the sensitivity of rats was tested and the dose-response curve for the apomorphine-induced hyperlocomotion determined. The dose of 1 mg/kg apomorphine exclusively induced in animals a locomotor activation. Stereotypies were not seen. After application of haloperidol, we observed a dose-dependent decrease in the apomorphine-induced hyperlocomotion (Fig. 3). The latter was antagonized by small doses of haloperidol, which had no effect on motility of controls.

ICV application of the β-casomorphin 5 derivatives led to a dose-dependent inhibition of the apomorphine hyperlocomotion, too. The strongest activity was found for D-Pip^{4}CM 5 (Fig. 2). Already, 5 nM D-Pip^{4}CM 5 inhibited the hypermotility completely, whereas 5 nM D-Phe^{3}CM 5 and 5 nM D-Pro^{4}CM 5 decreased it only to about 50%. These derivatives had also a depressive effect on exploratory activity. Also, the strongest inhibition was found using 5 nM D-Pip^{4}CM 5 to 20%. The exploratory activity was depressed by 10 nM D-Phe^{3}CM 5 to 35% and by relative high dosage of 40 nM D-Pro^{4}CM 5 to 15% (Fig. 1).

The situation is different concerning the des-Tyr casomorphin 5 derivatives. Although des-Tyr-CM 5 derivatives decreased the apomorphine-induced hypermotility, too, these was not a complete inhibition of hypermotility. The dose-activity curves were U-shaped, and the maximum inhibition was about 50%. The strongest effect was again observed with the D-Pip^{4}CM 5 derivative, 0.5 nM des-Tyr-D-Pip^{4}CM 5 decreased the apomorphine-induced hyperlocomotion to 46%, 1 nM des-Tyr-D-Pro^{4}CM 5 to 65%, and 5 nM of des-Tyr-D-

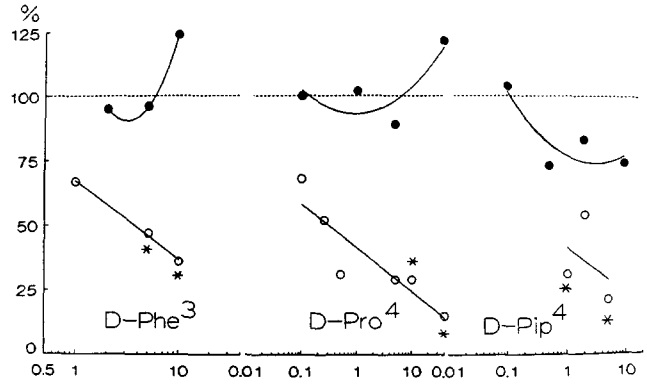

FIG. 1. Motility of casomorphins (○)- and des-Tyr-casomorphins (●)-treated animals during the first 5 min after application (motility of saline-injected animals = 100%). Abscissa, dosage in nM; *$p < 0.05$.

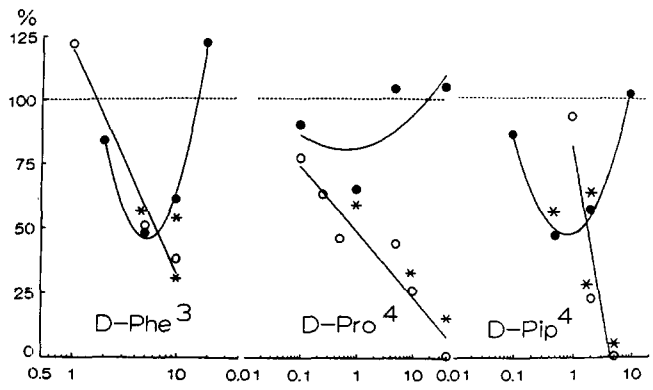

FIG. 2. Influence of casomorphins (○) and des-Tyr-casomorphins (●) on the hypermotility induced by 1 mg/kg apomorphine (apomorphine-induced motility = 100%). Abscissa, dosage in nM; $*p < 0.05$.

Phe^{3}CM 5 to 48% (Fig. 2). The exploratory activity was not significantly influenced by des-Tyr-D-Pip^{4}CM 5, des-Tyr-D-Phe^{3}CM 5, and des-Tyr-D-Pro^{4}CM 5 (Fig. 1).

DISCUSSION

The investigated β-casomorphin derivatives were found to have a more or less distinct inhibitory action on apomorphine-induced locomotor stimulation. After ICV applications, the tyrosine-containing opioid-like casomorphins caused a dose-dependent inhibition of the apomorphine hyperlocomotion. As opposed to this, only an incomplete inhibition was found using des-tyrosine casomorphin derivatives besides showing U-shaped dose-response curves. The decrease in apomorphine hyperlocomotion by casomorphin derivatives cannot be explained by the appearance of competing behavior due to a potentiation of apomorphine action because observations of animals never revealed stereotypies or catalepsies.

At first sight, the findings show a strong similarity between the dopamine receptor blocker haloperidol and the tyrosine-containing casomorphin 5 derivatives, suggesting a dopaminolytic effect. The results of Rauca and Matthies (29) and Kammerer et al. (15), however, speak against such a postsynaptic dopaminolytic action of β-casomorphin 5 peptides. As with apomorphine, unilateral intrastriatal application of these peptides caused a contralateral rotation in rats, whereas haloperidol evoked ipsilateral rotations. D-Pro^{4}CM 5 inhibits dopamine reuptake in the presynaptic nerve terminal and increases K^+-stimulated release of dopamine only in high concentrations. This presynaptic activity may be mediated via opiate receptors. Thus, the inhibitory influence of enkephalins and tyrosine-containing casomorphin opioid peptides, respectively, on the dopaminergic system could lead to an inhibition of the dopamine-induced hyperlocomotion.

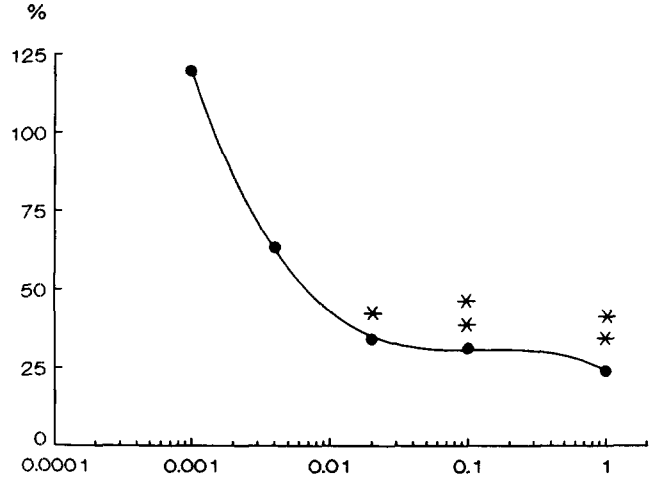

FIG. 3. Effect of haloperidol (IP) on hyperlocomotion induced by 1 mg/kg apomorphine. Abscissa, dosage in nM; $*p < 0.02$, $**p < 0.01$.

There are some references in the literature suggesting an interaction between opiates and dopamine in controlling locomotor activity (1,26,34). Thus, morphine and a potent enkephalin analog antagonized apomorphine-induced behavioral effects (32,28). It was demonstrated that opioids have significant antiapomorphine potency and this action is mediated at least in part by the nucleus accumbens, a mesolimbic region rich in dopamine. The nucleus accumbens' opioids tonically inhibit the release of dopamine (28).

Considering the varying strength of the effect of the tyrosine-containing CM 5 derivatives on apomorphine hyperlocomotion, it is highly probable that other mechanisms might be involved. A different occupation of receptor subpopulations as described for the analgetic activity (19) can also not be excluded. The clear differences in mode, duration, strength of action, and naloxone dependence upon the effect of morphine and various endorphins made Kameyama and Ukai (14) assume different affinities to the various opiate receptor subtypes, and the findings of Quock (27) indicate a more or less strong sensitivity and a differentiated distribution of opiate receptors.

Another explanation for the different strength of action of the tyrosine-containing casomorphin derivatives could be a GABAergic, serotonergic, and/or cholinergic modulation. Thus, dopamine-induced behavior may be either inhibited by 5-hydroxytryptamine (5-HT) or potentiated if the serotonergic transmission is disturbed (8).

The nonanalgetic des-tyrosine derivatives cannot be ascribed to an opiate receptor-mediated action. By reason of the lacking N-terminal amino acid tyrosine, the tetrapeptides have no affinity for opiate receptors. The absence of effect of naloxone on hypermotility induced by des-Tyr-y-endorphins is confirmatory evidence for a lack of affinity of these compounds for opiate receptors (14). The reduction in apomorphine hyperlocomotion is obviously not realized via postsynaptic dopamine receptors. According to the findings of Rauca and Matthies (29), the des-tyrosine peptides do not influence apomorphine-induced contralateral rotation after unilateral nigral lesion, but des-Tyr-D-Pro^{4}CM 5 and des-Tyr-D-Phe^{3}CM 5 counteracted the apomorphine-induced turning. These experiments seem to speak in favor of an action on presynaptic dopamine receptors. Similar findings are postulated for des-Tyr-y-endorphin. But, even if a blockade of postsynaptic dopamine receptors could not be demonstrated a postsynaptic inhibition cannot be completely excluded probably by influence on dopaminergic signal transduction. Nickolson and Berendsen suggested a modulating influence of des-Tyr-y-endorphin on dopaminergic activity in various apomorphine-induced behavioral patterns (22,23). Taking into account the apomorphine-inhibiting effect (37), an analogous mode of action can be supposed even for des-enkephalin-y-endorphin.

Because serotonin inhibits dopamine-induced behavior (8), we may hypothesize a serotonergic modulation. This suggestion was supported by finding a possibly serotonomimetic effect in the rat yawning behavior with des-Tyr-D-Pro^{4}CM 5 (30) and by biochemical results (15). Thus, it cannot be excluded that apomorphine-induced hyperlocomotion is reduced by tonic inhibition of dopaminergic neurons in the nucleus accumbens via serotonergic terminals.

During the total observation period, no great effect of the casomorphin derivatives by themselves on locomotor activity could be found compared to controls. However, all tyrosine-containing derivatives significantly attenuated the exploratory activity in the first 5 min after injection, whereas the des-tyrosine derivatives were without any effect. There is considerable confusion in the literature on the effects of endorphine derivatives. Kameyama and Ukai (14) reported an increased activity 15 min after ICV injections of des-Tyr-y-endorphin, whereas Nickolson (22) could not find an effect on open-field behavior. An ICV application of β-endorphin led to an increased locomotor activity (31). Stinius et al. (34) could also observe hyperlocomotion after injection of β-endorphin into the ventral tegmentum whereas Bloom et al. (3) and Kameyama and Ukai (14) found a decrease in locomotion after ICV injection. Bloom et al. (4), however, discovered hyperactivity and oral stereotypies immediately after ICV application of 5 μg β-endorphin; later, rats became inactive even with increasing doses. For morphine and DALA, biphasic motility curve was described (5,25).

This study demonstrates in each case a characteristic effect of the des-tyrosine derivatives on apomorphine-induced hyperlocomotion serving as model for hyperactivity of the dopaminergic system and corresponding pathophysiological events. Indeed, it is still an open question if these peptides exert their actions on pre- or postsynaptic sites. However, it is likewise easily possible that apomorphine-induced hyperlocomotion can be influenced by a direct or indirect action via other transmitter systems.

The dose–response curves of the des-tyrosine derivatives point to a limited maximum effect that could be an advantage in comparison to receptor blockers.

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