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NON-OPIATE β-ENDORPHIN FRAGMENTS AND DOPAMINE—II β-ENDORPHIN 2–9 ENHANCES APOMORPHINE-INDUCED STEREOTYPY FOLLOWING SUBCUTANEOUS AND INTRA-STRIATAL INJECTION

J. M. VAN REE

Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, 3521 GD Utrecht, The Netherlands

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Summary—The non-opiate β-endorphin (βE) fragment 2–16 (des Tyr^1-α-endorphin) enhanced apomorphine-induced stereotyped sniffing in rats, but did not interfere with the hypoactivity elicited by small doses of apomorphine. Structure–activity relationship studies revealed that the active moiety of α-endorphin fragments with respect to their potentiating effects on apomorphine-induced stereotyped sniffing resides in the βE fragment 2–9. Subsequent studies showed that the potentiating influence of βE 2–9 was dependent on the dose of the peptide and that the interaction between this peptide and apomorphine may be non-competitive in nature. The stereotyped sniffing elicited by apomorphine, injected bilaterally into the striatal area of the brain, was dose-dependently enhanced by intra-striatal pretreatment with βE 2–9. It is concluded that the influence of α-type endorphins and βE 2–9 on apomorphine-induced behavioural changes, is in some aspects opposite to that of γ-type endorphins, but may be mediated by quite different mechanisms.

Fragments of β-endorphin (βE) have been implicated in brain homeostatic processes. Among these are the non-opiate fragments of α- and γ-endorphin. γ-Type endorphins (e.g. des-Tyr^1-γ-endorphin (DTγE, β-E 2–17) and des-enkephalin-γ-endorphin (DEγE, β-E 6–17) have been found to induce behavioural effects which are in some aspect comparable to those of neuroleptic drugs (De Wied, Kovacs, Bohus, Van Ree and Greven, 1978; De Wied, Van Ree and Greven, 1980; Van Ree, Bohus and De Wied, 1980). α-Type endorphins (e.g. α-endorphin (αE, β-E 1–16) and des-Tyr^1-α-endorphin (DTαE, β-E 2–16) produced effects which were opposite to those of γ-type endorphins in a number of test paradigms and their influence on brain mechanisms has been compared to that of psychostimulant drugs like amphetamine (De Wied, 1978; Le Moal, Koob and Bloom, 1979; Van Ree *et al.*, 1980). These findings led to the postulate that the balance between γ-type and α-type endorphins may be physiologically important for brain function and that a disbalance may contribute to the symptomatology of patients suffering from schizophrenic psychosis (De Wied, 1978; Van Ree, Verhoeven, Van Praag and De Wied, 1978).

Since it has been proposed that the schizophrenic syndrome results from excess dopaminergic transmission in specific brain structures (Meltzer and Stahl, 1976; Van Praag, 1977; Van Kammen, 1979), it was of interest to study in detail the influence of α-type and γ-type endorphins on dopaminergic systems in the brain. Recently, it was found that γ-type endorphins attenuated the behavioural effects of small doses of the dopamine agonist apomorphine, but did not interfere with apomorphine-induced stereotypy (Van Ree, Innemee, Louwerens, Kahn and De Wied, 1982). The present study deals with the influence of α-type endorphins on behavioural changes elicited by apomorphine. It was found that these peptides, and particularly β-E 2–9, enhanced apomorphine-induced stereotyped sniffing, after systemic as well as intra-striatal injections.

Key words: α-endorphin, (des-Tyr^1)-α-endorphin, β-endorphin 2–9, apomorphine, stereotypy, striatum.

METHODS

Animals and test conditions

Male Wistar rats weighing 130–140 g were used. They were housed under controlled conditions with a 14:10 light–dark cycle (light on between 5.00 a.m. and 7.00 p.m.) and had free access to food and water. Experiments were carried out between 10.00 a.m. and 2.00 p.m. in a sound-attenuated room. Apomorphine and peptides were administered subcutaneously in the neck of the animals. Each animal was used only once.

For intrastriatal injections 60 rats were equipped with a stainless steel cannula at each site of the brain and aimed at the nucleus caudatus [coordinates 2.0 mm anterior to bregma, 6.0 mm below the skull and 2.5 mm lateral from the midline, according to Pellegrino and Cushman (1967)]. Details of the operation conditions have been presented previously (Van Ree and Wolterink, 1981). The rats were used three times with an interval between testing of at least one week. They were randomly allocated to the various treatment groups. After experiment the sites of injec-

tions were evaluated histologically as described before (Van Ree and Wolterink, 1981).

Two different test conditions were used: (A) Rectangular perspex observation cages (bottom 20 × 6.5 cm, height 32 cm). In this testbox, locomotor activity and rearing were counted for 3 min; (B) Circular perspex testcages (diameter 19.5 cm, height 28.5 cm). In this small open field, locomotor activity and rearing were counted and the duration (sec) of (stereotyped) sniffing was measured for 5 min. Details of the test conditions have been presented previously (Van Ree *et al.*, 1982).

α-Type endorphins and small doses of apomorphine

Groups of animals ($n = 6$) were treated with placebo (0.5 ml saline) or 50 μg αE, DTαE or DEαE and, after 1 hr were injected with placebo (0.2 ml saline) or apomorphine (25 or 125 μg/kg). Five minutes later, the rats were tested in the rectangular testbox (A) for 3 min.

DTαE and apomorphine-induced stereotypy

Groups of animals ($n = 11$–17) were injected with placebo (0.5 ml saline) or 50 μg DTαE and, after 1 hr, were injected with placebo (0.2 ml saline) or apomorphine (250 μg/kg). After 20 min, the rats were placed in the circular testbox (B) and the behaviour of the animals was observed for 5 min. In another experiment, groups of rats ($n = 6$) were treated with placebo or 50 μg DTαE and, after 1 hr, were injected with placebo. These rats were tested in the same way as outlined before.

Structure–activity relationships

Groups of animals ($n = 16$–18) were treated with placebo (0.5 ml saline) or 50 μg βE 2–9 or DEαE and, after 1 hr, were injected with apomorphine (250 μg/kg). Twenty minutes after the second injection, the rats were tested in testbox (B) for 5 min. In another experiment, the influence of βE 2–5 and βE 5–9 ($n = 6$–27) was investigated using the same test conditions. In a separate experiment, the influence of pretreatment with βE 2–9 was studied in rats receiving placebo treatment instead of apomorphine.

Dose-response relationships

Groups of animals ($n = 6$) were injected with placebo (0.5 ml saline) or 50 μg βE 2–9 and, after 1 hr, were treated with placebo (0.2 ml saline) or graded doses of apomorphine (125, 250, 500 μg/kg). Twenty minutes after the second injection, the rats were tested in testbox (B). Subsequently, groups of animals ($n = 8$) were treated with placebo (0.5 ml saline) or graded doses of βE 2–9 (25, 50, 100 μg) and, after 1 hr, were injected with 250 μg/kg apomorphine. Twenty minutes later, the rats were tested in testbox (B).

Intra-striatal treatment

Groups of animals ($n = 8$–10) equipped with cannulae into the striatal area were injected bilaterally

TABLE 1. Influence of different α-type endorphins on apomorphine-induced decrease of locomotion and rearing

Treatment dose (μg/kg)	Locomotion			Rearing		
	Placebo 0.5 ml	Apomorphine		Placebo 0.5 ml	Apomorphine	
		25	125		25	125
Placebo	11.9 ± 0.6† (14)	9.2 ± 0.3*** (14)	7.7 ± 0.8*** (6)	11.3 ± 0.8 (14)	7.7 ± 0.5*** (14)	3.2 ± 0.8*** (6)
α-Endorphin (βE 1–16)	13.0 ± 0.4 (6)	8.8 ± 0.5*** (6)	6.7 ± 0.9*** (6)	10.8 ± 1.2 (6)	7.2 ± 0.8* (6)	2.7 ± 1.1*** (6)
Des-Tyr[1]-α-endorphin (βE 2–16)	12.3 ± 1.0 (6)	8.5 ± 0.6** (6)	6.6 ± 0.7** (6)	13.4 ± 1.5 (6)	8.3 ± 0.6** (6)	2.6 ± 0.6*** (8)
Des-enkephalin-α-endorphin (βE 6–16)	12.5 ± 0.7 (14)	9.0 ± 0.4*** (14)	4.8 ± 0.9*** (6)	10.4 ± 1.1 (14)	6.7 ± 0.5** (14)	1.8 ± 0.7*** (6)

Rats were treated with placebo (0.5 ml saline) or 50 μg of peptide and after 1 hr with placebo (0.2 ml) or apomorphine (25 or 125 μg/kg). Five minutes after the last injection the rats were tested in a rectangular testbox for 3 min.

* Difference between placebo and apomorphine treatment (*$P < 0.05$, **$P < 0.01$, ***$P < 0.0001$).

† Mean ± SEM.

( ) Number of animals.

with placebo (1 μl saline) or βE 2–9 (1 ng dissolved in 1 μl saline) and after 1 hr with placebo (2 μl saline) or apomorphine (10 μg dissolved in 2 μl saline). Twenty minutes after the second injection, the rats were tested in testbox (B). Similar experiments were performed using other doses of βE 2–9 (i.e. 0.1, 10 and 1000 ng).

Analysis of the data

Groups mean ± SEM were calculated. Two tailed Student's *t*-tests were used for statistical analysis. One way analysis of variance (ANOVA) testing was performed on the data obtained with intrastriatal treatment.

Drugs and peptides

Apomorphine (apomorphine HCl) was obtained from O.P.G., Utrecht, The Netherlands. The following β-endorphin (βE) fragments were used: α-Endorphin (αE, βE 1–16); des-Tyr^1-α-endorphin (DTαE, βE 2–16); βE 2–9; βE 5–9; des-enkephalin-α-endorphin (DEαE, βE 6–16). They were kindly donated by Dr H. M. Greven, Organon International BV, Oss, The Netherlands. The purity of the peptides appeared to be 95–99%.

RESULTS

α-Type endorphins and small doses of apormorphine

Relatively small doses of apomorphine dose-dependently decreased the rate of locomotor activity and of rearing when the rats were tested 5 min after injection (Table 1). α-Endorphin did not influence the basal rate of ambulation or of rearing and did not affect the apomorphine-induced hypoactivity. Similar results were obtained with two non-opiate fragments of α-endorphin i.e. des-Tyr^1-α-endorphin and des-enkephalin-α-endorphin.

DTαE and apomorphine-induced stereotypy

Treatment with 250 μg/kg apomorphine resulted in a slightly increased rate of locomotor activity and decreased rate of rearing, but these effects did not reach statistical significance (Fig. 1). In addition, apomorphine induced stereotyped sniffing which lasted approximately half of the test time. The peptide DTαE increased the rate of locomotor activity and the duration of stereotyped sniffing in apomorphine-treated rats (Fig. 1). The peptide did not affect the basal of locomotor activity and rearing and the basal duration of sniffing (Table 2).

Structure-activity relationships

First, the effect of βE 2–9 and DEαE was explored. It was found that βE 2–9 mimicked the action of DTαE with respect to its potentiation of apomorphine-induced stereotypy (Fig. 2). However, in contrast to DTαE, βE 2–9 at this dose level did not increase the rate of locomotor activity in apomorphine-treated rats. The basal rate of sniffing was not affected by pretreatment with βE 2–9 (Table 2). The peptide DEαE did not affect the apomorphine-induced behavioural changes in this test paradigm.

The second experiment deals with fragments of βE 2–9, i.e.: βE 2–5 and βE 5–9. These peptides did not influence the behavioural changes elicited by apomorphine (Fig. 2). A slight, although not statistically significant increase in the rate of locomotor activity was found following treatment with βE 5–9.

Dose–response relationships

The stereotyped sniffing induced by apomorphine appeared to be related to the dose of the drug administered (Fig. 3). The duration of sniffing was somewhat shorter as compared to the experiments described before, probably due to seasonal variation in the sensitivity of the rats to apomorphine. At both dose levels of apomorphine (125 and 250 μg/kg) stereotyped sniffing was potentiated in rats pretreated with βE 2–9. This potentiation seems to follow the rules of a non-competitive interaction between the peptide and apomorphine. Locomotor activity and rearing were affected neither by apomorphine nor by additional peptide treatment (data not shown).

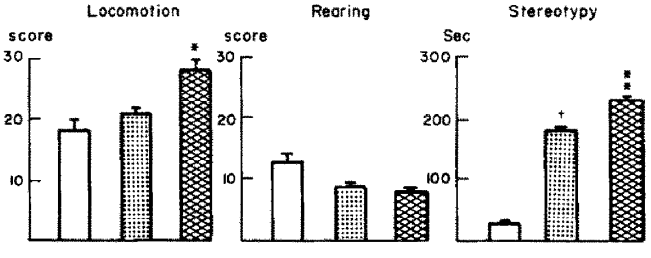

Fig. 1. The influence of des-Tyr^1-α-endorphin (DTαE, βE 2–16) on apomorphine-induced behavioural changes as assessed in a small open field. The rate of locomotion and rearing and the duration of (stereotyped) sniffing was measured for 5 min, beginning 20 min after subcutaneous treatment with placebo or apomorphine (250 μg/kg). Groups of animals were injected subcutaneously with placebo or DTαE (50 μg) 1 hr before apomorphine. Results are given as mean ± SEM (vertical bars). Treatments: □ placebo, placebo ($n = 11$); ▨ placebo, apomorphine ($n = 17$); ■ DTαE, apomorphine ($n = 17$). †Different from placebo, apomorphine treated rats (*$P < 0.01$, **$P < 0.001$). *Different from placebo, placebo treated controls ($P < 0.001$).

Table 2. The influence of pretreatment with 50 μg des-Tyr[1]-α-endorphin (DTαE) or β-endorphin 2–9 (βE 2–9) on the behaviour of rats treated with placebo as assessed in a small open field

Treatment (s.c.)		Number of animals	Locomotion score	Rearing score	Sniffing (sec)
−80 min	−20 min				
Placebo	Placebo	6	21.5 ± 2.9†	14.7 ± 2.9	28 ± 3
DTαE	Placebo	6	18.5 ± 1.4	12.2 ± 2.9	24 ± 2
βE 2–9	Placebo	6	18.7 ± 3.1	10.8 ± 1.7	24 ± 2

Testing lasted 5 min.
† Mean ± SEM.

Table 3. The influence of pretreatment with graded doses of β-endorphin 2–9 (βE 2–9) on apomorphine-induced behaviour changes as assessed in a small open field

Pretreatment (s.c.)	n	Locomotion score	Rearing score	Stereotyped sniffing (sec)
Placebo	8	32.6 ± 3.9†	8.9 ± 1.8	143 ± 6
25 μg βE 2–9	8	36.1 ± 3.8	11.6 ± 1.3	153 ± 4
50 μg βE 2–9	8	42.8 ± 3.4	11.8 ± 2.8	175 ± 10*
100 μg βE 2–9	8	53.1 ± 6.2*	15.1 ± 1.4*	189 ± 3**

Peptide was administered 80 min and apomorphine (250 μg/kg, s.c.) 20 min before testing, which lasted 5 min.
* Different from placebo pretreated rats (*$P < 0.02$, **$P < 0.001$).
† Mean ± SEM.

The potentiation of apomorphine-induced stereotypy was dependent on the dose of the peptide (Table 3). A dose of 25 μg appeared to be virtually inactive in this respect, while the potentiation elicited by 100 μg was greater than that following treatment with 50 μg βE 2–9. The largest dose tested also increased the rate of locomotor activity and rearing of the apomorphine-treated rats.

Intrastriatal treatment

Intrastriatal injection of 10 μg apomorphine did not affect the rate of locomotion and rearing of the animals, but induced stereotyped sniffing (Table 4). The fragment βE (2–9) (1 ng) enhanced the duration of stereotyped sniffing of the apomorphine-treated rats, but did not influence their rate of locomotion and rearing. Subsequent studies showed that the poten-

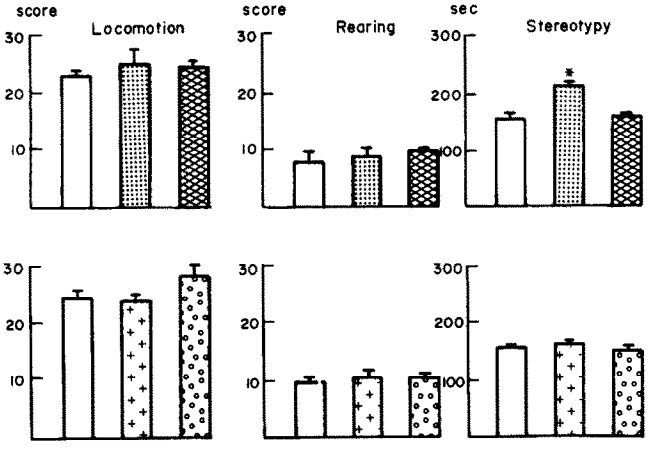

Fig. 2. The influence of different α-endorphin (βE 1–16) fragments on apomorphine-induced behavioural changes as assessed in a small open field. The rate of locomotion and rearing and the duration of stereotyped sniffing was measured for 5 min, beginning 20 min after subcutaneous treatment with apomorphine (250 μg/kg). Groups of animals were injected subcutaneously with placebo or peptide (50 μg) 1 hr before apomorphine. Results are given as mean ± SEM (vertical bars). Pretreatment: □ placebo ($n = 17$ and 27 for upper and lower panel respectively); ▨ βE 2–9 ($n = 18$); ▩ βE 6–16 ($n = 18$); ⊞ βE 2–5 ($n = 27$); ⊡ βE 5–9 ($n = 6$). *Different from placebo pretreated rats ($P < 0.001$).

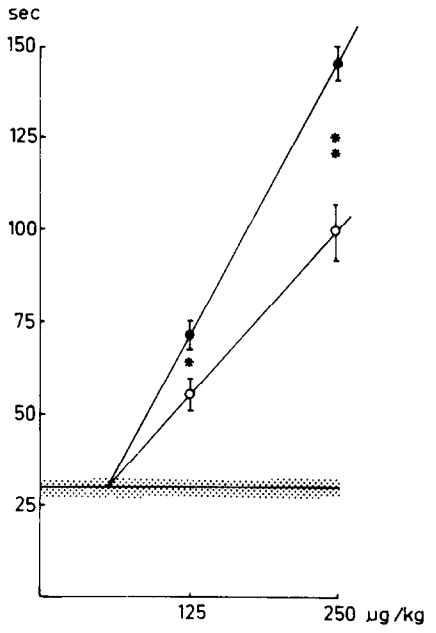

Fig. 3. The influence of pretreatment with β-endorphin 2–9 (βE 2–9) on apomorphine-induced stereotyped sniffing as assessed in a small open field. Testing was carried out for 5 min, beginning 20 min after subcutaneous treatment with placebo or apomorphine (125 or 250 μg/kg). Groups of animals ($n = 6$) were injected subcutaneously with placebo (○——○) or βE2–9 (50 μg, ●——●) 1 hr before apomorphine. Results are expressed as mean ± SEM (vertical bars) vs the dose of apomorphine. The shaded area represents the mean ± SEM of placebo, placebo injected controls. *Difference between pretreatment with peptide and placebo (*$P < 0.025$, **$P < 0.001$).

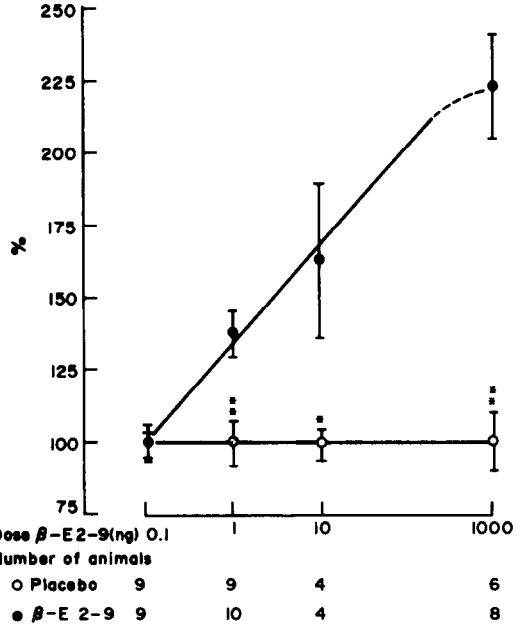

Fig. 4. The influence of pretreatment with graded doses of β-endorphin 2–9 (βE 2–9) on apomorphine-induced stereotyped sniffing when both substances were bilaterally injected into the nucleus caudatus. Groups of rats were injected with placebo (1 μl, ○) or βE 2–9 (0.1–1000 ng, ●) and after 1 hr with apomorphine (10 μg). Testing was carried out for 5 min, beginning 20 min after apomorphine treatment. Data are expressed as mean ± SEM (vertical bars), duration of stereotyped sniffing as percentage (%) of the mean value obtained in the placebo pretreated rats tested in the same experiment. *Difference between pretreatment with peptide and placebo (*$P < 0.05$, **$P < 0.001$).

tiating effect of the peptide on the apomorphine-induced stereotyped sniffing was dose-dependent (Fig. 4). Analysis of variance revealed that the 4 groups injected with placebo and apomorphine did not differ with respect to the duration of stereotyped sniffing (F: 1,05 (3,24)), while a significant effect in this respect was found between the groups injected with graded doses of βE 2–9 and apomorphine (F: 9,86 (3,27), $P < 0.01$). None of the doses of βE 2–9 significantly affected the basal rate of locomotion and rearing and the basal duration of sniffing (see Table 4 for the 1 ng dose).

DISCUSSION

The present data show that DTαE and βE 2–9 potentiated apomorphine-induced stereotypy, while α-type endorphins, including DTαE, did not affect the hypoactivity elicited by small doses of apomorphine.

Table 4. The effect of pretreatment with 1 ng β-endorphin 2–9 (βE 2–9) on apomorphine-induced behavioural changes, when both substances were bilaterally injected into the nucleus caudatus

Treatment			Locomotion	Rearing	Stereotyped sniffing
−60 min	0 min	n	score	score	(sec)
Placebo	Placebo	8	29.1 ± 2.6†	15.0 ± 1.8	27.5 ± 2.5
Placebo	Apomorphine		27.9 ± 2.8	12.9 ± 1.8	47.8 ± 3.9‡
βE 2–9	Placebo	8	28.0 ± 3.3	11.9 ± 2.1	29.0 ± 2.9
βE 2–9	Apomorphine	10	36.3 ± 4.7	13.0 ± 2.7	65.8 ± 4.1*‡

Locomotion, rearing and (stereotyped) sniffing were measured for 5 min at 20 min after injection with placebo (1 μl saline) or apomorphine (10 μg).

* Different from placebo, apomorphine treated rats ($P < 0.01$).

† Mean ± SEM.

‡ Different from placebo instead of apomorphine treated rats ($P < 0.001$).

Considering the concept of multiple dopamine receptors, i.e. DA_1 vs DA_2, DA_3, DA_4; DA_e vs DA_1; postsynaptic vs presynaptic (Carlsson, 1975; Cools and Van Rossum, 1980; Kebabian and Calne, 1979; Seeman, 1980), which has been discussed before in relation to effects of apomorphine in rats (Van Ree *et al.*, 1982) it might be that α-type endorphins and βE 2–9 interfere somehow with the action of apomorphine on postsynaptically located dopamine receptor systems (probably DA_e receptors). An interference by these peptides with presynaptically located dopamine receptors is unlikely, because these receptors have been implicated in apomorphine-induced hypoactivity and this effect of apomorphine was not affected by α-type endorphins. Interestingly, opposite effects were observed with γ-type endorphins (Van Ree *et al.*, 1982). These peptides attenuated the apomorphine-induced hypoactivity, while they did not change the stereotyped sniffing elicited by apomorphine. Thus, the influence of α-type endorphins and βE 2–9 and that of γ-type endorphins on apomorphine-induced behavioural changes, although opposite in some aspects, may be mediated by quite different mechanisms. Firstly, the effects of apomorphine (hypoactivity vs stereotypy) are suggested to be mediated by different dopaminergic mechanisms located in the nucleus accumbens and nucleus caudatus respectively (Kelly, Seviour and Iversen, 1975; Kelly and Iversen, 1976; Pijnenburg, Honig, Van der Heyden and Van Rossum, 1976; Costall, Marsden, Naylor and Pycock, 1977). Accordingly, apomorphine injected into the striatum induced stereotyped sniffing without changing the rate of locomotion and this apomorphine-induced effect was potentiated by intrastriatal injection of βE 2–9. Secondly, different dopamine receptors are concerned in the apomorphine-induced behavioural changes i.e. presynaptic receptors with respect to hypoactivity vs postsynaptic and/or DA_e receptors with respect to stereotypy. Thirdly, the interference by γ-type endorphins with the effects of apomorphine was of a competitive nature, while that of βE 2–9 may be described as non-competitive. This non-competition interaction suggests that the mode of action of βE 2–9 with respect to its potentiation of apomorphine-induced stereotypy is different from that of apomorphine itself.

Little is known about the interference between α-type endorphins and brain dopamine, which hampers the discussion about the mode of action of these peptides. Subcutaneously injected α-endorphin facilitated the rate of self-stimulation elicited via electrodes implanted in the ventral tegmental-medial substantia nigra area, where the cell bodies of the mesostriatal dopaminergic pathways are located (Dorsa, Van Ree and De Wied, 1979). Since α-endorphin did not affect the self-stimulation elicited via electrodes implanted in the nucleus accumbens area (Van Ree and Otte, 1980), dopamine systems other than those of the nucleus accumbens (e.g. the nigrostriatal system) may be involved in the effect of α-endorphin on self-stimulation. This agrees well with the present finding on the influence of βE 2–9 on apomorphine-induced stereotypy, when both substances are injected into the striatum. Intracerebroventricularly administered α-endorphin and DTαE decreased the dopamine disappearance following α-methyl-*p*-tyrosine treatment in a selected number of brain nuclei (Versteeg, De Kloet and De Wied, 1979; Versteeg, Kovacs, Bohus, De Kloet and De Wied, 1982). In particular, intra-diencephalic dopamine systems seem to be affected, but with respect to DTαE, no effect was found in the nucleus caudatus and the nucleus accumbens. Thus, at present it is not possible to locate the site of action of α-type endorphins, either in terms of pre- or postsynaptic dopaminergic elements, or in terms of a direct or an indirect (transsynaptic) action on dopamine neurones.

While the active moiety of γ-type endorphins with respect to their interference with apomorphine-induced behavioural changes is present in the C-terminal region (i.e. in the 6–17 region of β-endorphin), that of α-type endorphins is in the N-terminal region, since βE 2–9 mimicked the action of DTαE on stereotyped sniffing elicited by apomorphine. Smaller fragments like βE 2–5 and βE5–9 appeared to be inactive in this respect. The influence of α-type endorphins on apomorphine-induced stereotypy is apparently not related to the opiate action of α-endorphin, since the amino acid tyrosine (1) is essential for opiate activity, but not for the interference with apomorphine.

The present findings favour the concept that fragments of β-endorphin play a role in brain homeostatic processes and particularly in processes in which dopamine transmission is concerned. Consequently, it might be that an altered fragmentation of β-endorphin into α- and/or γ-type endorphins (Burbach, Loeber, Verhoef, Wiegant, De Kloet and De Wied, 1980) can be implicated in those psychopathological disturbances in which dopamine transmission may be enhanced or reduced (i.e. schizophrenia and Parkinsonism). In particular, the balance between α-type and γ-type endorphins may be of importance in this respect. However, it must be kept in mind that the present data revealed that both the site and mode of action of α-type endorphins and βE 2–9 are quite different from those of γ-type endorphins (see Van Ree *et al.*, 1982).

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