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NON-OPIATE β-ENDORPHIN FRAGMENTS AND DOPAMINE—VI

BEHAVIOURAL ANALYSIS OF THE INTERACTION BETWEEN γ-TYPE ENDORPHINS AND DOPAMINERGIC SYSTEMS IN THE NUCLEUS ACCUMBENS OF RATS

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Summary—Injection of small doses of apomorphine, bromocriptine and the new ergoline compound, GYKI-32887 into the nucleus accumbens decreased locomotor activity when rats were tested in a small open field. This effect was observed following injection of 1 pg of these substances; GYKI-32887 being more potent than bromocriptine. The hypolocomotion induced by the ergoline compound could be prevented by local pretreatment with haloperidol (30 pg), fluphenazine (30 pg), sulpiride (10 pg) or desenkephalin-γ-endorphin (DEγE; 100 pg). Large doses of apomorphine and amphetamine, injected into the nucleus accumbens, increased locomotor activity. This behavioural response was antagonized by pretreatment with haloperidol (30 pg), but not with sulpiride (10 pg) or DEγE (100 pg or 10 ng). It is concluded that two dopaminergic receptor systems exist in the nucleus accumbens with different sensitivity to apomorphine. One of these receptor systems, which is activated by small doses of apomorphine and ergoline compounds, can be blocked by classical and atypical neuroleptics and by the neuroleptic-like peptide DEγE. This may be of relevance to the antipsychotic action of these substances.

Key words: nucleus accumbens, dopamine receptor system, neuroleptics, locomotor activity, desenkephalin-γ-endorphin, γ-type endorphins, bromocriptine.

The β-endorphin (βE) fragment, γ-endorphin [βE-(1–17)] induces morphine-like effects and has actions in behavioural experiments which resemble those of neuroleptic drugs (De Wied, Kovács, Bohus, Van Ree and Greven, 1978; Király, Tapfer, Borsy and Gráf, 1981). Subsequent studies revealed that the non-opiate fragments of γ-endorphin, e.g. des-Tyr^1-γ-endorphin [DTγE, βE-(2–17)] and desenkephalin-γ-endorphin [DEγE, βE-(6–17)] had a neuroleptic-like action in a number of behavioural test-procedures (De Wied *et al.*, 1978; De Wied, Van Ree and Greven, 1980). In order to investigate the mode of action of γ-type endorphins, studies were focussed on dopamine in brain, since neuroleptic drugs are potent dopamine antagonists (Niemegeers and Janssen, 1979). Behaviourally, the anti-dopaminergic action of neuroleptics is generally established by analysing the effects against the dopamine agonists apomorphine and amphetamine. Small doses of apomorphine and other dopamine receptor agonists such as the ergot derivative bromocriptine, caused behavioural changes (e.g. hypoactivity) which are opposite to those elicited by large doses (e.g. stereotypy, motor stimulation). It has been postulated that the sedation and decreased locomotor activity caused by these compounds are due to stimulation of presynaptically located dopamine receptor systems and consequently to decreased dopaminergic activity, while the stimulatory motor effects and stereotypy are due to activation of postsynaptically located receptor systems (Carlsson, 1975; Di Chiara, Corsini, Merne, Tissari and Gessa, 1978; Strömbom, 1977; Skirboll, Grace and Bunney, 1979; Costall, Fortune, Hui and Naylor, 1980).

A series of previous studies dealing with systemic treatment have revealed that γ-type endorphins antagonized the behavioural effects induced by small doses of apomorphine and did not affect those observed after injection with large doses of this drug (Van Ree, Innemee, Louwerens, Kahn and De Wied, 1982a). Subsequently, it was found that a dopaminergic system is present in the nucleus accumbens which can be activated by small doses of apomorphine, resulting in hypoactivity of the rats (Van Ree and Wolterink, 1981) and that this hypoactivity can completely be antagonized by intraaccumbal pretreatment with γ-type endorphins, as well or with the dopamine antagonists, haloperidol and sulpiride (Van Ree, Caffé and Wolterink, 1982b).

The present experiments were designated to further characterize the dopaminergic system in the nucleus accumbens which is sensitive to small doses of apomorphine and γ-type endorphins and to explore the specificity of γ-type endorphins with respect to the

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different dopaminergic systems present in the nucleus accumbens.

METHODS

Animals

Male Wistar rats, weighing 130–140 g at the time of operation, were used. They were equipped with a stainless-steel cannula (0.6 mm outer diameter, 0.3 mm inner dia) at each side of the brain and aimed at the nucleus accumbens. The coordinates of the point of penetration were 2.6 mm anterior to bregma and 2.7 mm lateral to the midline. The cannulae were inserted at an angle of 12° to 6.1 mm below the dura. After operation the rats were housed in separate cages. In general, the rats were used three times with an interval of 1 week. Details of the operation and housing conditions have been reported previously (Van Ree and Wolterink, 1981).

Experimental procedure

At least 7 days after operation the behavioural testing started. The rats were injected bilaterally with 1 μl using a Hamilton syringe by inserting a needle (0.25 mm outer dia) into the guide cannula. In most experiments two injections were given, spaced by a time interval of 40 min: first, an injection with a neuroleptic drug, DEγE or placebo and secondly, an injection with a dopamine agonist or placebo. Twenty minutes after the last injection the rats were placed in a small open field, a Perspex circular test cage (diameter 19.5 cm, height 28.5 cm), the bottom of which was divided into 4 equal sections. Locomotor activity was measured for 3 min by counting the number of sections explored and the duration of sniffing was determined in seconds. In addition in some experiments, the locomotor activity and frequency of grooming was measured 5 min after the last injection. For this behavioural observation the rats were placed in a small Perspex rectangular observation cage (bottom 20 × 6.5 cm, height 32 cm) for 3 min. Locomotor activity was measured by counting the number of crossings over the midline and the frequency of grooming by counting every start of a grooming episode.

Experiment 1. Dopamine agonists and hypoactivity

Groups of animals ($n = 4 - 13$) were injected with saline (1 μl) or graded doses of bromocriptine (0.001–1000 ng) or GYKI-32887 (0.001–0.1 ng) and after 5 min, tested in the small Perspex rectangular testcage. The rats were tested again at 20 min after injection in the small open field.

Experiment 2. Antagonism of small doses of dopamine agonists

Groups of animals ($n = 4 - 21$) were injected with saline (1 μl), haloperidol (30 pg), fluphenazine (30 pg), sulpiride (10 pg) or DEγE (100 pg) and after 40 min with either apomorphine (10 ng), bromocriptine (100 pg) or GYKI-32887 (10 pg). The rats were tested in the small open field at 20 min after the last injection.

Experiment 3. Antagonism of large doses of dopamine agonists

Groups of animals ($n = 4 - 36$) were injected with saline (1 μl), haloperidol (30 pg), sulpiride (10 pg) or DEγE (100 pg or 10 ng), and after 40 min with placebo, apomorphine (10 μg) or amphetamine (1 or 2 μg). The rats were tested in the small open field at 20 min after the last injection.

Histological control

After the experiments the sites of injection were evaluated histologically as described previously (Van Ree and Wolterink, 1981). Data obtained from rats with cannulae outside the nucleus accumbens were discarded from further analyses.

Data analysis and statistics

Groups means and standard error were calculated and the statistical significance was determined using analysis of variance (ANOVA) and subsequently by Student's t-test.

Drugs and peptides

Apomorphine (Apomorphine–HCl), amphetamine (Dexamphetamine sulphate), haloperidol (Haldol®) and sulpiride (Dogmatil®) were obtained from O.P.G. Utrecht, The Netherlands. Bromocriptine (Parlodel®) was a product of Sandoz Ltd, Basel, Switzerland. Fluphenazine (Moditen®) was purchased from Squibb & Sons Ltd, England. Desenkephalin-γ-endorphin [DEγE, βE-(6–17)] was donated by Organon International B.V., Oss, The Netherlands. The purity of the peptide appeared to be 95–99%. The new ergoline derivative, GYKI-32887 originated from the Institute for Drug Research, Budapest, Hungary. Its chemical structure is: 8-(*N*-2-azido-ethyl-*N*-methane-sulphonylamino)-methyl-6-methyl-8-ergolen bimaleate. It was synthesized by Dr E. Magó-Karácsony (for effects of this compound on behaviour of rats see Borsy, Király, Magó-Karácsony, Berzétei and Bagdy, 1984).

RESULTS

The site of injection appeared to be bilateral and in the middle and anterior part of the medial section of the nucleus accumbens, as reported previously (Van Ree and Wolterink, 1981). In none of the experiments was a significant change observed in the frequency of grooming or the duration of sniffing by any of the treatments.

Dopamine agonists and hypoactivity

Both bromocriptine and GYKI-32887 decreased locomotor activity when behavioural testing was performed at 5 and 20 min after injection (Fig. 1).

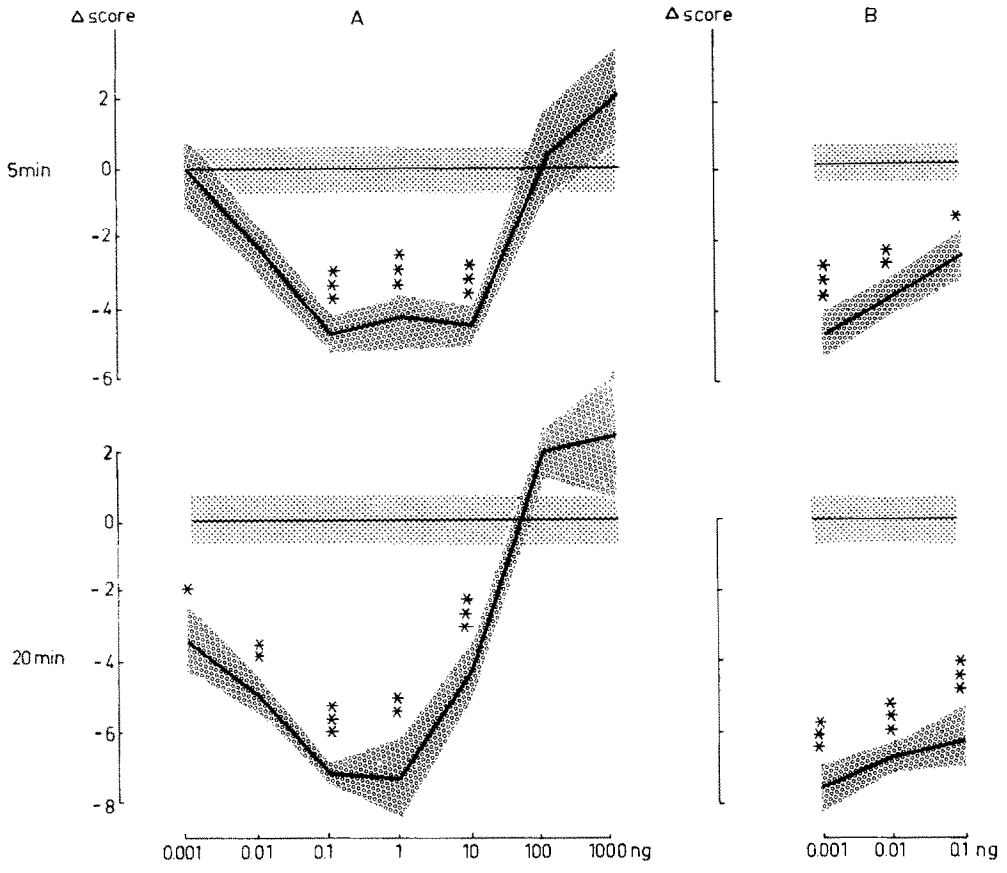

Fig. 1. Locomotor activity of animals injected with saline or graded doses of bromocriptine (A) or GYKI-32887 (B) into the nucleus accumbens. The rats were tested at 5 min after injection in the rectangular test box and at 20 min after injection in the small open field. The results are depicted as the difference (Δ score) between the score of the saline- and the drug-treated rats ($n = 4$–9) against the dose of drug-treated rats (ng). The shaded areas represent 2 SEM (dots—saline, open circles—drug). The mean ($\pm$SEM) of the scores of the saline-treated rats ($n = 18$) were 12.8 ± 0.5 and 17.9 ± 0.7 at 5 and 20 min after injection, respectively. Analysis of variance (ANOVA) testing revealed for bromocriptine $F(6.32)$: 10.4 and 19.4 and for GYKI-32887 $F(3.19) = 9.3$ and 24.5 for the results obtained at 5 and 20 min after injection respectively. *Difference between saline- and drug-injected animals (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

Even the smallest dose of bromocriptine (1 pg) induced a significant effect. The maximum effect of this substance was observed after injection of approx. 0.1–1 ng. The drug GYKI-32887 was even more potent than bromocriptine in decreasing locomotor activity; the smallest dose used (1 pg) being the most effective. Comparing these data with those previously found with apomorphine, it appeared that bromocriptine was about 100 times and GYKI-32887 at least 10,000 times more potent than apomorphine in inducing this behavioural effect (Van Ree and Wolterink, 1981). The dose–effect curve of bromocriptine followed a U-shaped function and was similar to the one observed previously for apomorphine (Van Ree and Wolterink, 1981). The present data do not allow a similar conclusion to be drawn with respect to GYKI-32887, although the 0.1 ng dose was less effective than 1 pg of this substance.

Antagonism of small doses of dopamine agonists

For these experiments the following doses of the dopamine agonists were selected: apomorphine 10 ng, bromocriptine 100 pg and GYKI-32887 10 pg. For the dopamine antagonist a dose was selected (haloperidol and fluphenazine 30 pg and sulpiride 10 pg) which was somewhat smaller than the dose that interferes with locomotor activity *per se* as revealed from pilot experiments. The DEγE was injected in a dose of 100 pg, an effective dose in antagonizing apomorphine-induced hypolocomotion (Van Ree *et al.*, 1982b). Haloperidol and sulpiride were not tested against apomorphine, since previous studies had shown that these drugs completely antagonized the hypolocomotion induced by apomorphine (Van Ree *et al.*, 1982b). The dopamine antagonists and DEγE did not significantly affect the locomotor activity of saline-treated rats (Table 1). Apomorphine, bromocriptine and GYKI-32887 consistently decreased locomotor activity. This hypolocomotion was prevented by pretreatment with the neuroleptics haloperidol, fluphenazine and sulpiride and with the peptide DEγE. In fact, the rats treated with neu-

Table 1. Effects of haloperidol, fluphenazine, sulpiride and desenkaphalin-γ-endorphin (DEγE) on hypolocomotion induced by apomorphine, bromocriptine or GYKI-32887, following bilateral injection into the nucleus accumbens of rats

Treatment				Locomotor activity score (mean ± SEM)	n
−60 min		−20 min			
(A)					
Placebo		Placebo		19.7 ± 0.4	24‡
Haloperidol	30 pg	Placebo		19.0 ± 1.5	5
Fluphenazine	30 pg	Placebo		17.0 ± 1.5	4
Sulpiride	10 pg	Placebo		18.2 ± 0.8	5
DEγE	100 pg	Placebo		18.4 ± 1.0	5
(B)					
Placebo		Placebo		19.7 ± 0.4	24‡
Placebo		Apomorphine	10 ng	13.5 ± 0.7*	11
Fluphenazine	30 pg	Apomorphine	10 ng	26.3 ± 1.1††	6
DEγE	100 pg	Apomorphine	10 ng	21.0 ± 0.8††	5
(C)					
Placebo		Placebo		19.7 ± 0.4	24‡
Placebo		Bromocriptine	100 pg	15.5 ± 0.3*	14
Haloperidol	30 pg	Bromocriptine	100 pg	18.2 ± 1.4†	6
Fluphenazine	30 pg	Bromocriptine	100 pg	24.6 ± 1.0††	5
Sulpiride	10 pg	Bromocriptine	100 pg	20.8 ± 1.0††	6
DEγE	100 pg	Bromocriptine	100 pg	19.5 ± 0.6††	6
(D)					
Placebo		Placebo		19.7 ± 0.4	24‡
Placebo		GYKI-32887	10 pg	14.7 ± 0.6*	10
Haloperidol	30 pg	GYKI-32887	10 pg	19.5 ± 0.9††	5
Fluphenazine	30 pg	GYKI-32887	10 pg	22.0 ± 1.7††	6
Sulpiride	10 pg	GYKI-32887	10 pg	20.8 ± 1.1††	5
DEγE	100 pg	GYKI-32887	10 pg	17.7 ± 1.0†	6

Locomotor activity was assessed in a small open field for 3 min.

Analysis of variance: A: $F(4.38) = 2.1$ (ns); B minus placebo, placebo: $F(2.19) = 59.9$ ($P < 0.01$); C minus placebo, placebo: $F(4.32) = 20.3$ ($P < 0.01$); D minus placebo, placebo: $F(4.27) = 9.8$ ($P < 0.01$). All groups treated with placebo at −60 min: $F(3.55) = 36.8$ ($P < 0.01$).

*Different from placebo, placebo-treated rats ($P < 0.001$). †Different from placebo, dopamine agonist-treated rats (†$P < 0.02$; ††$P < 0.001$). n = Number of rats. ‡The same rats.

roleptics, except fluphenazine or DEγE, together with the dopamine agonists, did not differ from rats treated twice with saline. With fluphenazine it was observed that combined treatment of this neuroleptic with a dopamine agonist led to a significant increase of locomotor activity.

Antagonism of large doses of dopamine agonists

For these studies, the direct acting drug apomorphine and the indirect acting drug amphetamine were selected as dopamine agonists and, as dopamine antagonists, haloperidol and sulpiride and the peptide DEγE. Apomorphine, injected in a dose of 10 μg, increased locomotor activity (Table 2). Pretreatment with haloperidol (30 pg) prevented this apomorphine-induced hyperactivity, while neither sulpiride (10 pg) nor DEγE (10 ng) significantly affected this behavioural response. Amphetamine (1 and 2 μg) dose-dependently increased locomotor activity (Table 2). This response was antagonized by pretreatment with haloperidol, but not with sulpiride. Tested at two dose levels (100 pg and 10 ng) DEγE did not decrease the amphetamine-induced hyperlocomotion. In contrast, 10 ng of DEγE significantly potentiated the hyperlocomotion induced by 1 μg of amphetamine.

DISCUSSION

The present data agree with previous findings that small doses of apomorphine, injected into the nucleus accumbens of rats, decreased locomotor activity and that this decrease could be prevented by pretreatment with desenkephalin-γ-endorphin (Van Ree *et al.*, 1982b). To further characterize this receptor system, the D2-dopaminergic receptor agonist bromocriptine, according to the classification of Kebabian and Calne (1979) was tested. It was found that this drug, like apomorphine, dose-dependently decreased locomotor activity; the dose–response curves of both substances followed a U-shaped function. However, bromocriptine was about 100 times more potent than apomorphine in this respect. The hypolocomotion induced by apomorphine (Van Ree *et al.*, 1982b) and bromocriptine could be prevented by preteatment with the D2-antagonist sulpiride (according to Kebabian and Calne, 1979). Thus, it seems likely that apomorphine induces hypolomotion by activation of D2-dopaminergic receptor system. The new ergoline derivative, GYKI-32887, mimicked the action of bromocriptine and was even more potent in this respect, indicating that ergolines are very effective in stimulating the D2-dopaminergic receptor system. As with apomorphine, the hypolocomotion

Table 2. Effects of haloperidol, sulpiride and desenkephalin-γ-endorphin (DEγE) on hyperlocomotion induced by apomorphine (A) or amphetamine (B), following bilateral injection into the nucleus accumbens of rats

Treatment				Locomotor activity score (mean ± SEM)	n
−60 min		−20 min			
(A)					
Placebo		Placebo		17.7 ± 0.7	7
Placebo		Apomorphine	10 μg	23.5 ± 0.8*	10
Haloperidol	30 pg	Apomorphine	10 μg	17.5 ± 1.2†	6
Sulpiride	10 pg	Apomorphine	10 μg	21.2 ± 0.9	6
DEγE	10 ng	Apomorphine	10 μg	21.9 ± 1.1	10
DEγE	10 ng	Placebo		16.1 ± 0.5	11
(B)					
Placebo		Placebo		16.4 ± 0.5	34
Placebo		Amphetamine	1 μg	19.0 ± 0.6*	35
Haloperidol	30 pg	Amphetamine	1 μg	19.6 ± 1.0	5
Sulpiride	10 pg	Amphetamine	1 μg	22.2 ± 1.0	4
DEγE	100 pg	Amphetamine	1 μg	19.5 ± 0.6	6
DEγE	10 ng	Amphetamine	1 μg	22.0 ± 0.9†	22
Placebo		Amphetamine	2 μg	25.3 ± 0.7*	26
Haloperidol	30 pg	Amphetamine	2 μg	20.2 ± 1.0†	5
Sulpiride	10 pg	Amphetamine	2 μg	25.4 ± 0.9	7
DEγE	100 pg	Amphetamine	2 μg	25.2 ± 0.5	6
DEγE	10 ng	Amphetamine	2 μg	25.6 ± 2.0	12

Locomotor activity was assessed in a small open field for 3 min.
Analysis of variance: A: $F(5.44) = 12.8$ ($P < 0.01$); B: $F(10.151) = 15.1$ ($P < 0.01$). *Different from placebo, placebo treated rats ($P < 0.001$). †Different from placebo, apomorphine or placebo, amphetamine-treated rats ($P < 0.005$). n = number of rats.

induced by bromocriptine and GYKI-32887 could be prevented by small doses of haloperidol, fluphenazine and DEγE. This further supports the hypothesis that hypolocomotion is indeed mediated by a dopaminergic system and that this system is affected by the neuroleptic-like peptide DEγE.

Large doses of apomorphine and amphetamine, injected into the nucleus accumbens, increased locomotor activity. This action is probably mediated by dopaminergic receptor systems, since a small dose of haloperidol antagonized this behavioural response. Apomorphine may directly activate this receptor system, while the action of amphetamine may be indirect, via release of endogenous dopamine (Fuxe and Ungerstadt, 1970). This receptor system however seems to be less sensitive to sulpiride, since a dose of this drug that effectively prevented the hypolocomotion induced by apomorphine, bromocriptine and GYKI-32887 did not interfere with the hyperlocomotion induced by apomorphine or amphetamine. Also, DEγE had a differential action on the hypo- and hyperlocomotion responses. While 100 pg of this peptide completely antagonized the hypolocomotion induced by the dopamine agonists, this and a 100 times larger dose did not decrease the hyperlocomotion produced by apomorphine and amphetamine. Thus, the two dopaminergic receptor systems present in the nucleus accumbens may be blocked by haloperidol, while sulpiride and DEγE predominantly antagonized the receptor system activated by small doses of apomorphine and ergoline compounds. This agrees with previous findings dealing with systemic administration and concerning the interaction between haloperidol, sulpiride and DEγE and apomorphine-induced behavioural changes (Van Ree *et al.*, 1982b; Serra, Van Ree and De Wied, 1983).

Besides the subclassification of dopaminergic receptor sytems as D1 and D2 systems according to Kebabian and Calne (1979), other subclassifications have been proposed. Seeman (1980) has classified the receptor systems on basis of binding data as D1, D2, D3 and D4 receptor sites. Since the receptor system mediating hypolocomotion is sensitive to small doses of dopamine agonists and antagonists, this receptor system can be regarded as a D4 receptor site. The system mediating hyperlocomotion seems to be sensitive to large doses of dopamine agonists and small doses of dopamine antagonists and may therefore be classified as a D2 receptor site, according to the proposal of Seeman (1980). Thus, DEγE may specifically interfere with the D4 receptor system in the nucleus accumbens.

Another classification is based on the localization of the receptor system, i.e. presynaptic or postsynaptic (Carlsson, 1975; Di Chiara *et al.*, 1978; Strömbom, 1977; Skirboll *et al.*, 1979; Costall *et al.*, 1980). Activation of presynaptic sites results in a diminished dopamine output, leading to decreased dopaminergic activity. This could explain the differential action of apomorphine, assuming that apomorphine can activate more potently the presynaptically located receptor sites. According to this classification, DEγE and sulpiride interfere with presynaptically, rather than postsynaptically, located receptor systems. Such an action of DEγE could explain the slight potentiation of the amphetamine-induced hyperlocomotion. However, it should be kept in mind that the two dopaminergic receptor systems, activated by small and large doses of apo-

morphine, can also belong to different dopaminergic systems which have a different sensitivity to apomorphine.

In conclusion, the receptor system in the nucleus accumbens, activated by small doses of apomorphine, and sensitive to γ-type endorphins could be regarded as a D2 receptor (Kebabian and Calne, 1979), as a D4 receptor (Seeman, 1980) or as a presynaptically located receptor. In addition to this classification, it is of interest that a dopamine receptor system exists in the nucleus accumbens that can be, at least functionally, antagonized by the classical neuroleptics, haloperidol and fluphenazine, atypical neuroleptics sulpiride and clozapine (Van Ree *et al.*, 1982b) and the neuroleptic-like peptides, γ-type endorphins. All these substances have been shown to be potentially antipsychotic (Van Ree, Verhoeven, De Wied and van Praag, 1982c). Moreover, dopaminergic systems in the nucleus accumbens have been implicated in schizophrenic psychosis (Crow, 1979). Thus, it may be postulated that the receptor system in the nucleus accumbens which is activated by small doses of apomorphine may mediate the antipsychotic action of neuroleptic drugs and the γ-type endorphins.

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