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# NON-OPIATE β-ENDORPHIN FRAGMENTS AND DOPAMINE—III γ-TYPE ENDORPHINS AND VARIOUS NEUROLEPTICS COUNTERACT THE HYPOACTIVITY ELICITED BY INJECTION OF APOMORPHINE INTO THE NUCLEUS ACCUMBENS

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**Summary**—The hypoactivity in rats induced by small doses of apomorphine, injected bilaterally into the nucleus accumbens area of the brain, could be antagonized by pretreatment with the neuroleptic-like neuropeptide des-enkephalin-γ-endorphin (DEγE, β-endorphin 6–17) as well as with the neuroleptic drugs haloperidol, sulpiride and clozapine injected into the accumbens. Dose-response studies revealed that a dose of 100 pg DEγE completely inhibited the apomorphine-induced hypomotility. The influence of DEγE appeared to be specific for γ-type endorphins, since α-type endorphins were inactive in this respect. Treatment with DEγE injected into the accumbens for 4 days resulted in an enhancement of apomorphine-induced hypoactivity. It is concluded that γ-type endorphins may control the activity of dopaminergic transmission in the nucleus accumbens, a suggestion which may be of significance for the purported neuroleptic-like and antipsychotic action of γ-type endorphins.

It has been postulated that dopaminergic hyperactivity in the brain plays a key role in the pathogenesis of schizophrenic psychoses (Mattysse, 1974; Meltzer and Stahl, 1976; Van Praag, 1977; Van Kammen, 1979). Accordingly, most neuroleptic drugs currently used to treat schizophrenic patients are potent blockers of dopamine (DA) activity (Creese, Burt and Snyder, 1976; Seeman, Lee, Chau-Wong and Wong, 1976; Niemegeers and Janssen, 1979). Although these drugs exert their blocking action in most, if not all, brain DA systems, it has been suggested that their antipsychotic activity may be related to their influence on the mesolimbic DA system. The cell bodies of this system are located in the ventral tegmental-medial area of the substantia nigra and their terminals in several nuclei of the limbic forebrain, including the nucleus accumbens (Anden, 1972; Crow, Deakin and Longden, 1977; Crow, 1979; Matthysse, 1974). Thus it seemed worthwhile to study the interaction between antipsychotic drugs and dopamine systems which are present in the area of the nucleus accumbens.

Recently it was observed that γ-type endorphins i.e. des-Tyr$^1$-γ-endorphin (DTγE, β-endorphin (βE) 2–17) and des-enkephalin-γ-endorphin (DEγE, βE 6–17), which have been found to possess neuroleptic-like activity in rats (De Wied, Kovacs, Bohus, Van Ree and Greven, 1978; De Wied, Van Ree and Greven, 1980) and anti-psychotic action in humans (Verhoeven, Van Praag, Van Ree and De Wied, 1979; Van Ree, De Wied, Verhoeven and Van Praag, 1980), interfere with the behavioural effects of small doses of the DA agonist apomorphine following subcutaneous treatment (Van Ree, Innemee, Louwerens, Kahn and De Wied, 1982). Thus, the hypoactivity induced by small doses of apomorphine was inhibited by acute treatment with γ-type endorphins and enhanced following subchronic treatment with these peptides. This effect was specific with respect to the peptide structure and with respect to the DA receptor systems involved in this particular action of apomorphine, since α-type endorphins appear to be inactive in this respect (Van Ree, 1982) and apomorphine-induced stereotypy was not affected by γ-type endorphins (Van Ree *et al.*, 1982). Since the mesolimbic DA projections to the nucleus accumbens have been implicated in the control of locomotion (Costall, Naylor, Cannon and Lee, 1977; Pijnenburg, Honig and Van Rossum, 1975; Pijnenburg, Honig, Van der Heyden and Van Rossum, 1976), and small doses of apomorphine induced hypoactivity when injected into the nucleus accumbens area (Van Ree and Wolterink, 1981), the interaction between γ-type endorphins and this apomorphine-induced effect was analysed in detail. For these studies DEγE, which has been shown to be the shortest sequence of γ-type endorphins with full neuroleptic-like activity in rats was selected (De Wied *et al.*, 1980; Van Ree *et al.*, 1982).

Key words: γ-type endorphins, des-enkephalin-γ-endorphin, apomorphine, neuroleptic-like action, dopamine, nucleus accumbens, hypoactivity, haloperidol, sulpiride, clozapine.

## METHODS

### *Animals and test conditions*

Male rats of a Wistar strain, weighing 130–140 g at the time of operation, were used. They were equipped with a stainless steel cannula at each site of the brain and aimed at the nucleus accumbens. Details of the operation and housing conditions have been presented previously (Van Ree and Wolterink, 1981). After bilateral injections, the rats were tested in two different test cages exactly similar to those described previously (Van Ree and Wolterink, 1981). Briefly, 5 min after the last injection, the rats were placed in a small perspex rectangular testbox (box I) and locomotion and rearing was measured for 3 min. The rats were tested again at 20 min after injection in a perspex circular test cage and the same behavioural elements were observed for 3 min. Each animal was used only once. After the experiment the sites of injection were evaluated histologically as described before (Van Ree and Wolterink, 1981). Data from rats with cannulae outside the nucleus accumbens were discarded from the analyses.

### *DEγE apomorphine-induced hypo-activity*

Groups of animals ($n = 6$) were injected bilaterally with placebo (1 μl saline) or DEγE (100 pg dissolved in 1 μl saline) and after 40 min with placebo (1 μl saline) or apomorphine (10 ng dissolved in 1 μl saline). Locomotor activity and rearing of the rats were measured at 5 and 20 min after injection in the rectangular and round testbox respectively.

### *Dose–response relationships*

Groups of animals ($n = 5$–26) were injected with placebo (1 μl saline) or graded doses of DEγE (3–10,000 pg) and after 40 min with placebo (1 μl saline) or apomorphine (10 ng). Testing was performed as outlined before. Subsequently, groups of animals ($n = 6$) were injected with placebo (1 μl saline) or 100 pg DEγE and after 40 min with placebo (1 μl saline) or apomorphine (3 ng) and tested at 5 and 20 min after the last injection.

### *Structure–activity relationships*

Groups of animals ($n = 6$–7) were injected with placebo (1 μl saline), DTγE (10 ng) or DTαE (10 ng) and after 40 min with placebo (1 μl saline) or apomorphine (3 ng). Testing was performed as outlined before.

### *Chronic treatment with DEγE*

Groups of animals ($n = 6$–12) were injected with placebo (1 μl saline) or DEγE (10 ng) twice daily (at 10.00 a.m. and 5.00 p.m.) for 4 days. On the 5th day the animals were injected (10.00–12.00 a.m.) with placebo (1 μl) or apomorphine (3 ng) and tested at 5 and 20 min after the last injection.

### *Various neuroleptic drugs*

Groups of animals ($n = 6$–9) were injected with placebo (1 μl saline) or a neuroleptic drug and after 40 min with placebo (1 μl saline) or apomorphine (10 ng). Locomotor activity of the rats was measured at 5 and 20 min after injection in the rectangular testbox and round box respectively. In different experiments the effect of 10 pg haloperidol, 10 pg sulpiride and 100 ng clozapine was tested. In an additional experiment 100 ng clozapine was injected 90 min before placebo or apomorphine treatment.

### *Data analysis and statistics*

Groups means and standard errors were calculated and the statistical significance was determined using Student's *t*-test.

### *Drugs and peptides*

Apomorphine (apomorphine HCl), haloperidol (Haldol$^{R}$) and sulpiride (Dogmatil$^{R}$) were obtained from O.P.G. Utrecht (The Netherlands) and clozapine from Sandoz (Basel, Switzerland). The following β-endorphin (βE) fragments (Dr H. M. Greven, Organon International b.v., Oss, the Netherlands) were used: des-Tyr$^{1}$-γ-endorphin (DTγE, βE 2–17), des-enkephalin-γ-endorphin (DEγE, βE 6–17) and des-Tyr$^{1}$-α-endorphin (DTαE, βE 2–16). The purity of the peptides appeared to be 95–99%.

## RESULTS

The site of injections appeared to be bilaterally and in the middle and anterior part of the medial section of the nucleus accumbens, as reported before (Van Ree and Wolterink, 1981).

### *DEγE and apomorphine-induced hypo-activity*

As reported previously (Van Ree and Wolterink, 1981), 10 ng apomorphine injected bilaterally into the nucleus accumbens area resulted in a decreased rate of locomotion and rearing both at 5 min and 20 min after injection (Fig. 1). This effect of apomorphine was inhibited by pretreatment with 100 pg of DEγE. In fact, locomotion and rearing of the pretreated rats did not differ from those of animals treated with placebo only. Injection with DEγE *per se* did not affect the rate of locomotion and rearing of the rats.

### *Dose–response relationship*

Although a slight decrease in locomotion was found following injection with 100 or 10,000 pg DEγE into the nucleus accumbens as compared to placebo treatment, this difference did not reach statistical significance. Even a dose of 25 μg of this peptide did not significantly affect the rate of locomotion and rearing (data not shown). The inhibitory effect of DEγE on apomorphine-induced hypomotility, as assessed at 20 min after administration of apomorphine, appeared to be dose-related (Fig. 2). Similar effects as depicted in Figure 2 were found for the rate of locomotion and rearing at 5 min and for the rate of rearing at 20 min after apomorphine treatment. A relatively large dose

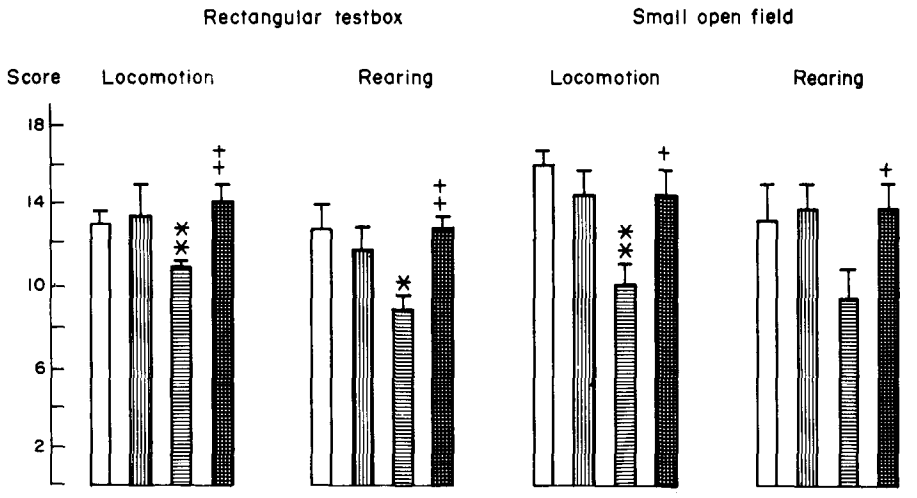


Fig. 1. The influence of pretreatment with DEγE ($\beta E_{6-17}$) on the apomorphine-induced hypomotility when both substances were bilaterally injected into the nucleus accumbens. Locomotion and rearing were measured for 3 min, at 5 min (rectangular testbox) and 20 min (small open field) after injection with placebo (1 μl saline) or apomorphine (10 ng). Animals were treated with placebo (1 μl saline) or DEγE (100 pg) 40 min before apomorphine. The mean locomotion and rearing scores of 6 animals per treatment groups are presented. Vertical bars indicate SEM. Treatments: □ placebo, placebo; ▥ DEγE, placebo; ▤ placebo, apomorphine; ■ DEγE, apomorphine. * Different from placebo, placebo treated rats (* $P < 0.05$, ** $P < 0.01$). † Different from placebo, apomorphine treated rats († $P < 0.05$, †† $P < 0.01$).

of 10 ng DEγE also prevented the effects of apomorphine (Fig. 2). In a subsequent experiment it was observed that pretreatment with DEγE (100 pg) inhibited the hypomotility induced by 3 ng of apomorphine (rate of locomotion at 20 min after injection: [placebo–apomorphine 9.3 ± 1.0; DEγE-apomorphine 13.8 ± 0.5; $P < 0.005$]). A similar effect was found for 25 μg of DEγE (data not shown).

*Structure–activity relationship*

Injection of the des-Tyr analogue of γ-endorphin and α-endorphin i.e. DTγE and DTαE into the nu-

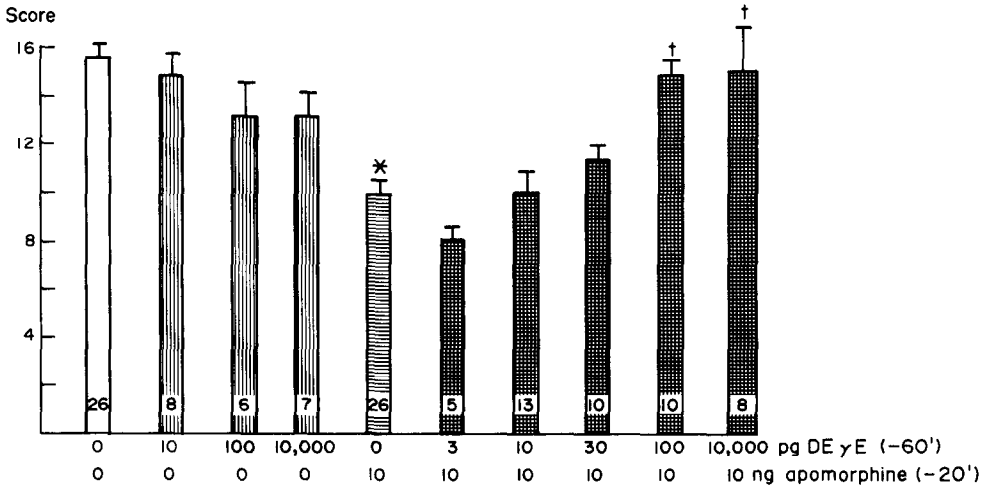


Fig. 2. The influence of graded doses of DEγE on the apomorphine-induced hypomotility when both substances were bilaterally injected into the nucleus accumbens, as assessed in a small open field 20 min after injection with placebo (1 μl saline) or apomorphine (10 ng). Animals were treated with placebo (1 μl saline) or different doses of DEγE ranging from 3 to 10,000 pg 60 min prior to testing. The mean locomotion score ± SEM (vertical bars) are presented. The number of animals per group are depicted in the columns. Treatments: □ placebo, placebo; ▥ DEγE, placebo; ▤ placebo, apomorphine; ■ DEγE, apomorphine. * Different from placebo, placebo treatment ($P < 0.001$). † Different from placebo, apomorphine treatment ($P < 0.001$).

Table 1. The effect of pretreatment with 10 ng DTαE ($\beta E_{2-16}$) or DTγE ($\beta E_{2-17}$) on the apomorphine-induced hypomotility when both substances were bilaterally injected into the nucleus accumbens

| Treatment | | Rectangular testbox | | Small open field | |
|---|---|---|---|---|---|
| −40 min | 0 min | Locomotion | Rearing | Locomotion | Rearing |
| Placebo | Placebo | 13.3 ± 0.6† | 12.3 ± 0.7 | 13.5 ± 0.8 | 11.3 ± 1.4 |
| DTαE | Placebo | 13.7 ± 0.6 | 12.3 ± 0.7 | 12.7 ± 0.3 | 11.7 ± 0.9 |
| DTγE | Placebo | 13.6 ± 1.0 | 11.6 ± 0.8 | 12.7 ± 0.5 | 11.0 ± 1.0 |
| Placebo | Apomorphine | 11.0 ± 0.7* | 8.7 ± 0.9** | 10.9 ± 0.7* | 8.9 ± 0.8 |
| DTαE | Apomorphine | 10.6 ± 0.5** | 8.0 ± 1.0** | 10.4 ± 0.5** | 8.1 ± 0.9* |
| DTγE | Apomorphine | 12.3 ± 0.6 | 12.0 ± 1.0 | 12.1 ± 0.6 | 11.6 ± 1.3 |

Locomotion and rearing were measured for 3 min at 5 min (rectangular testbox) and 20 min (small open field) after injection with placebo (1 μl saline) or apomorphine (3 ng).
* Different from treatment with placebo instead of apomorphine (*$P < 0.05$ **$P < 0.01$).
† Mean ± SEM of 6–7 animals per group.

cleus accumbens did not modify the rate of locomotion or rearing of rats treated with placebo 5 or 20 min before testing (Table 1). However, pretreatment with DTγE (10 ng) attenuated the apomorphine-induced hypomotility. In contrast, DTαE appeared to be inactive in this respect. In fact, apomorphine elicited a similar degree of hypomotility in DTαE pretreated rats as that found in placebo pretreated controls.

*Chronic treatment with DEγE*

Intra-accumbens treatment with DEγE for 4 days did not markedly influence the rate of locomotion. However, the rate of rearing appeared to be lower in the DEγE-treated rats as compared to that of placebo-treated controls, especially when tested in the rectangular testbox (Fig. 3).

Injection of apomorphine into the accumbens in placebo-pretreated rats induced a significant decrease in the rate of locomotion as well as that of rearing both at 5 min and 20 min after injection. Rats pretreated with DEγE appeared to be more sensitive to apomorphine, in that a more marked hypomotility was observed following injection with apomorphine. This enhanced responsiveness to apomorphine treatment was statistically significant at 20 min after apomorphine injection.

*Various neuroleptic drugs*

Pretreatment with 10 pg haloperidol injected into

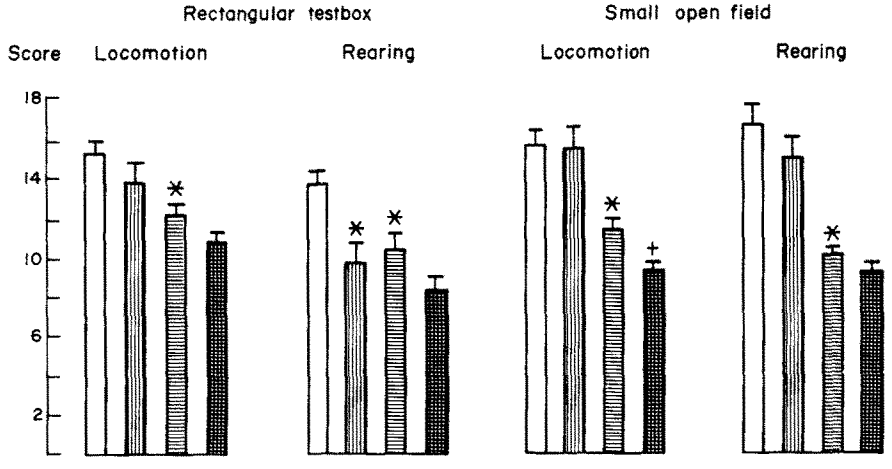


Fig. 3. The influence of subchronic treatment with DEγE ($\beta E_{6-17}$) on the apomorphine-induced hypomotility when both substances were bilaterally injected into the nucleus accumbens. Locomotion and rearing was measured for 3 min at 5 min (rectangular testbox) and 20 min (small open field) after injection with placebo (1 μl saline) or apomorphine (3 ng). Animals were pretreated twice daily for 4 days with placebo (1 μl saline) or DEγE (10 ng). The mean ± SEM (vertical bars) locomotion and rearing score of each treatment group are presented. Treatments: □ placebo, placebo ($n = 11$); ▥ DEγE, placebo ($n = 6$); ▤ placebo, apomorphine ($n = 12$); ■ DEγE, apomorphine ($n = 11$). * Different from placebo, placebo treated rats ($P < 0.01$). † Different from placebo, apomorphine treated rats ($P < 0.01$).

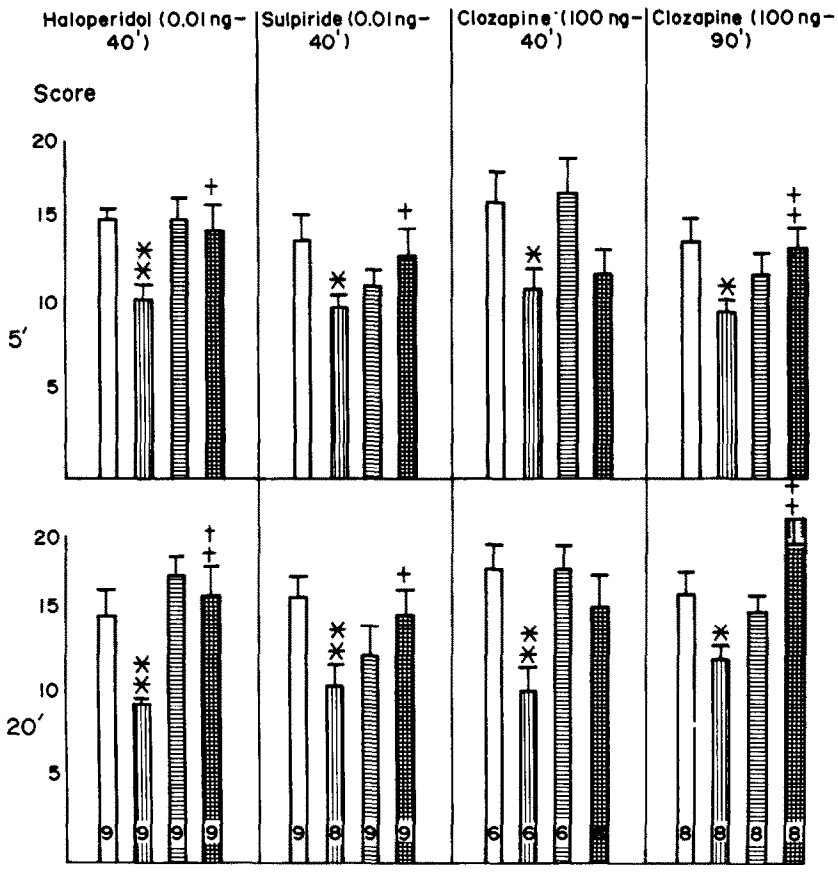


Fig. 4. The influence of pretreatment with different neuroleptics (haloperidol, sulpiride, clozapine) on the apomorphine-induced hypomotility when the drugs were bilaterally injected into the nucleus accumbens. Locomotion was measured for 3 min, at 5 min (rectangular testbox) and 20 min (small open field) after injection with placebo (1 μl saline) or apomorphine (10 ng). Animals were treated with placebo (1 μl saline) or the indicated neuroleptic drug (0.01 or 100 ng) 40 min (−40') or 90 min (−90') before apomorphine The mean locomotion score per treatment group is presented. Vertical bars indicate SEM. The number of animals per group is depicted in the columns. Treatments: □ placebo, placebo; ▤ neuroleptic, placebo; ▥ placebo, apomorphine; ■ neuroleptic, apomorphine. * Different from placebo, placebo treated rats (* $P < 0.05$, ** $P < 0.01$). † Different from placebo, apomorphine treated rats († $P < 0.05$; †† $P < 0.01$).

the accumbens completely inhibited the apomorphine-induced hypoactivity, while this amount of haloperidol did not affect locomotion of placebo-treated animals (Fig. 4). The same was found following injection of 10 pg sulpiride. This dose of sulpiride caused a slight, although not significant, decrease of locomotion in placebo-treated rats (Fig. 4). A somewhat different effect was found for clozapine. Injection of this drug (100 ng) 40 min before apomorphine did not or partly inhibit the apomorphine- induced hypoactivity when the rats were tested at 5 and 20 min after treatment with apomorphine respectively. However, when clozapine was given 90 min before apomorphine a complete inhibition of apomorphine-induced hypoactivity was observed. In fact, the inhibition of apomorphine-induced hypoactivity was related to the time between treatment with clozapine and testing (Fig. 4). In general, similar effects as described for locomotion were found with respect to the rate of rearing of the animals.

## DISCUSSION

The present data favour the nucleus accumbens as the site of interaction between the neuroleptic-like and antipsychotic neuropeptide (des-enkephalin)-γ-endorphin (DEγE) and apomorphine. Injection of DEγE into the nucleus accumbens prevented the hypomotility induced by apomorphine injected into the accumbens. Similar observations were done previously following subcutaneous treatment of these entities (Van Ree *et al.*, 1982). Thus, it is conceivable that DEγE attenuates behavioural changes elicited by small doses of apomorphine by a direct or indirect interference with dopamine (DA) systems present in the nucleus accumbens. The DA projections to the

nucleus accumbens originate from the ventral tegmental-medial area of the substantia nigra (i.e. A10 cell bodies) and are part of the mesolimbic or mesostriatal DA pathways (Lindvall and Björklund, 1978). Evidence has been presented that DA activity in the nucleus accumbens is implicated in the control of locomotion, in that a higher activity leads to an increased locomotion (Fink and Smith, 1980; Costall, Hui and Naylor, 1980; Pijnenburg *et al.*, 1976).

Since small doses of apomorphine may act preferentially on presynaptically located DA receptors (Di Chiara, Porceddu, Vargiu, Argiolas and Gessa, 1976; De Chiara, Corsini, Mereu, Tissari and Gessa, 1978; Strömbom, 1977; Corsini, Del Zempo, Manconi, Piccardi, Onali and Mangoni, 1977; Tamminga, Schaffer, Smith and Davis, 1978; Skirboll, Grace and Bunney, 1979) it has been proposed that the hypoactivity induced by injection of apomorphine into the accumbens is due to stimulation of these receptor sites, resulting in a decreased DA release, although other explanations are possible (Van Ree and Wolterink, 1981). The present data indicate that this effect of apomorphine is attenuated by DE$\gamma$E following local injection, which may suggest that this neuropeptide directly or indirectly blocks presynaptically located DA receptors. Such a blockade may eventually lead to an increased DA release.

Chronic treatment with DE$\gamma$E resulted in an increased sensitivity to apomorphine, which may suggest that the DA receptors mediated apomorphine-induced hypomotility have become supersensitive. Also in this respect, the action of DE$\gamma$E resembles that of other DA receptor blocking substances (Muller and Seeman, 1978). Thus, (sub)chronic treatment with DE$\gamma$E may eventually lead to a decreased dopaminergic transmission in the nucleus accumbens. However, such a decreased DA output should be established before definite conclusions can be drawn in this respect.

The influence of DE$\gamma$E seems to be specific for $\gamma$-type endorphins, since DT$\gamma$E mimicked the action of DE$\gamma$E while DT$\alpha$E was not active. Also, other data suggest that the nucleus accumbens is a sensitive site for $\gamma$-type endorphins. Thus, electrical self-stimulation elicited from the ventral tegmental-medial area of the substantia nigra as well as from the nucleus accumbens was attenuated by subcutaneous treatment with DT$\gamma$E (Dorsa, Van Ree and De Wied, 1979; Van Ree and Otte, 1980). Injection into the accumbens of relatively large doses of DT$\gamma$E, like DPI and ergometrine, attenuated the excessive grooming response elicited by intracerebroventricularly administered $ACTH_{1-24}$ (Cools, Wiegant and Gispen, 1978; Gispen, Ormond, Ten Haaf and De Wied, 1980) and inhibited the increased locomotor activity induced by injection of methylphenidate into the accumbens (Davis, Samuel, Mathe and Mohs, 1981). Similar, and even smaller, doses of DT$\gamma$E as used in the present study have been shown to attenuate passive avoidance behaviour when the peptide was injected into the nucleus accumbens (Kovacs, Telegdy and De Wied, 1982). Interestingly, these doses are in the range of the amount of $\gamma$-type endorphins present in the nucleus accumbens as assessed using a specific radioimmunoassay procedure (Dorsa, Majumdar and Chapman, 1981). Thus, it might be concluded that $\gamma$-type endorphins may have a physiological function in controlling the activity of dopaminergic transmission in the nucleus accumbens. Since chronic treatment may decrease dopaminergic activity in this area as pointed out before, a chronic deficiency may result in a hyperactivity of these DA systems. This fits well with the postulated link between the $\gamma$-type endorphins and the dopamine hypothesis of schizophrenia (Van Ree *et al.*, 1982). In fact, disturbances in the mesolimbic DA systems and particularly those projecting to the nucleus accumbens have been implicated in the pathogenesis of schizophrenia (Crow, 1979). Thus, the antipsychotic action of $\gamma$-type endorphins may be the result of an interference by these peptides with the DA activity in the nucleus accumbens area. The same may hold for the antipsychotic action of neuroleptics, since the classical neuroleptic, haloperidol, as well as the atypical neuroleptics, sulpiride and clozapine, mimic the action of $\gamma$-type endorphins in antagonizing the apomorphine-induced hypoactivity. The time delay with respect to the effectiveness of clozapine may indicate that this drug exerts its action in an indirect manner. Of particular interest is the dose of haloperidol and sulpiride i.e. 10 pg, which is active in this respect. Since the interaction between apomorphine and these drugs is obtained with small doses of both the agonist and the antagonist it might be postulated that DA receptor sites that are particularly sensitive to small doses of both agonists and antagonists (D4 receptors according to the classification of Seeman, 1980) are involved. However, little is known as yet about the characteristics and localization of these receptors, apart from the fact that they can bind dopamine agonists and antagonists at nanomolar concentrations. Nevertheless, the present data suggest that the four antipsychotic substances tested ($\gamma$-type endorphins, haloperidol, sulpiride and clozapine) directly or indirectly interfere with a dopaminergic system in the nucleus accumbens, which may be located presynaptically and/or characterized as sensitive to small doses of both agonists and antagonists. This suggestion may have important consequences for refining the dopamine hypothesis of schizophrenia and for the mode of antipsychotic action of both neuroleptics and $\gamma$-type endorphins.

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