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NON-OPIATE β-ENDORPHIN FRAGMENTS AND DOPAMINE—V γ-TYPE ENDORPHINS AND PROLACTIN SECRETION IN RATS

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Summary—The effects on prolactin secretion of three peptide-derivatives of β-endorphin which show neuroleptic-like activities in rats were studied.

Intravenous administration of γ-endorphin (β-endorphin (βE) 1–17) enhanced plasma prolactin levels. γ-Endorphin did not affect the prolactin secretion by hemipituitary glands incubated *in vitro* and by cultured pituitary cells, but it reversed, in a dose-dependent way, the dopamine-induced inhibition of prolactin release. This effect of γ-endorphin could be prevented by co-incubation with the opiate-antagonist naloxone.

In vivo studies with non-opiate-like fragments of γ-endorphin, des-Tyr[1]-γ-endorphin (DTγE, βE 2–17) and des-enkephalin-γ-endorphin (DEγE, βE 6–17), showed that these peptides suppressed the plasma prolactin levels, when prolactin release was slightly stimulated. However, DEγE dose-dependently enhanced plasma prolactin levels, when prolactin release was low. Subchronic treatment with DEγE for 4 days made prolactin release more sensitive to the inhibitory action of small doses of apomorphine. Neither DTγE nor DEγE affected prolactin release by hemipituitary glands and cultured pituitary cells. They did also not affect the dopamine-induced inhibition of prolactin release *in vitro*.

It is suggested that γ-endorphin increases prolactin secretion by interfering with dopaminergic systems in the pituitary and that DTγE and DEγE have a modulatory action on prolactin secretion.

It has long been recognized that patients receiving large doses of neuroleptic drugs develop hyperprolactinemia and occasionally galactorrhea and/or amenorrhea (MacLeod, 1976). Most of these neuroleptic drugs are dopamine-receptor blocking agents (Anden, Dahlstrom, Fuxe and Hökfelt, 1966). The sustained increase in serum prolactin (PRL) levels following the administration of drugs like haloperidol, pimozide and perphenazine is probably mediated via a direct inhibitory action on dopamine-receptors on the prolactin-secreting cells in the pituitary gland (MacLeod, 1976; MacLeod and Lehmeyer, 1974).

In the present study the effects on prolactin secretion were evaluated in the rat of γ-endorphin (β-endorphin (βE) 1–17, (des-Tyr[1])-γ-endorphin (DTγE, βE 2–17) and des-enkephalin-γ-endorphin (DEγE, βE 6–17)), three peptides with neuroleptic-like activity in rats (De Wied, Kovacs, Bohus, Van Ree and Greven, 1978a; De Wied, Van Ree and Greven, 1980). Both DTγE and DEγE have also been shown to have antipsychotic effects in man (Verhoeven, Van Praag, Van Ree and De Wied, 1979; Van Ree, De Wied, Verhoeven and Van Praag, 1980a). At first the effect of *in vivo* administration of these peptides on circulating prolactin levels was evaluated. Thereafter direct effects on prolactin secretion by hemipituitary glands incubated *in vitro* and by cultured normal pituitary cells and on the dopamine-mediated inhibition of prolactin release *in vitro* were investigated.

METHODS

Animals. In the experiments in which the *in vivo* effects of the peptides were investigated, male white Wistar strain rats weighing between 160 and 180 g were used. For intracerebroventricular injection the rats were equipped with plastic canulae in one of the lateral brain ventricles about 1 week prior to experimentation. The rats were housed with *ad libitum* food and water conditions. The light was on from 5 a.m. to 7 p.m. in the animal house. The rats were killed by decapitation and plasma was used for prolactin determination. For the *in vitro* experiments anterior pitui-

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taries were obtained from 180–220 g female Wistar rats.

Drugs. The following peptides were used: β-endorphin and the β-endorphin (βE) fragments γ-endorphin (βE 1–17), des-Tyr[1]-γ-endorphin (DTγE, βE 2–17), des-enkephalin-γ-endorphin (DEγE, βE 6–17) and α-endorphin (βE 1–16). These peptides were dissolved in one drop of 0.01 N HCl and further diluted with saline or artificial CSF. They were administered in a volume of 0.5 ml or 1 μl, when given systematically or intraventricularly, respectively. Apomorphine HCl (OPG, Utrecht, the Netherlands) was dissolved in saline.

Pituitary incubations. Each incubation flask contained three hemipituitaries (each from a separate animal), incubated in 1 ml tissue culture medium 199 (Gibco Bio-Cult, Glasgow, Scotland). After a 30 min preincubation the medium was replaced and the drugs were added. The flasks were incubated at 37°C in a Dubnoff shaker in an atmosphere of 95% O_2–5% CO_2 (v/v). After a 5 hr incubation, the medium was removed and the pituitaries were weighed. All incubations were carried out in plastic vials, while the serial dilution steps of the peptide-solutions were also done in plastic tubes.

Pituitary cells. Anterior pituitary glands of 12 female rats were minced and chopped and incubated for 120 min with dispase (2.4 U/ml; Boehringer, Mannheim, Western Germany). The dispersed cells were cultured for 4 days in Eagle's minimal essential medium and 10% foetal calf serum. Thereafter the effect of the peptides on prolactin release by the fixed cells was investigated for 4 hr.

Hormone determination. The prolactin content of the incubation medium was measured by a double antibody radioimmuno assay (RIA) using materials and protocols supplied by the NIAMDD Rat Pituitary Hormone Distribution Program. The results are expressed in terms of NIAMDD Rat PRL RP-1.

Statistics. The results are expressed as the mean ± SEM, and statistical analysis of the *in vivo* studies was performed by Student's unpaired *t*-test and of the *in vitro* studies by analysis of variance (one-way classification, as described by Snedecor and Cochran, 1969).

RESULTS

The effect of parenteral administration of the peptides on the plasma prolactin concentration was studied in several experiments (Table 1). Intravenous administration of 50 μg β-endorphin and 50 μg γ-endorphin resulted in an increase of plasma levels of prolactin 20 min after injection, while α-endorphin did not affect the circulating concentration of prolactin (Table 1A). Intracerebroventricular administration of 0.5 μg of β-endorphin induced hyperprolactinemia after 30 min, while the other peptides were not effective (Table 1B). The non-opiate like fragments of γ-endorphin, DTγE and DEγE suppressed plasma levels of prolactin, when these levels were slightly stimulated by the intravenous injection procedure (Table 1A and C). A similar, but more pronounced, inhibitory effect was observed following treatment with naloxone (Table 1C). Under conditions in which prolactin levels were low, it was found that subcutaneous administration of DEγE induced a dose-dependent increase of plasma prolactin concentration 80 min after injection (Fig. 1).

Table 1. Effect of the parenteral administration of β-endorphin and its fragments on plasma concentrations of prolactin (PRL)

(A) The effect of the intravenous administration of 50 μg of α-, β-, γ-endorphin and DTγE on plasma prolactin. The animals were decapitated 20 min after injection.

	Plasma PRL (ng/ml)
Saline (0.5 ml)	70 ± 15
α-Endorphin (50 μg)	69 ± 9
β-Endorphin (50 μg)	111 ± 13*
γ-Endorphin (50 μg)	125 ± 19*
DTγE (50 μg)	32 ± 3*

(B) The effect of the intracerebroventricular administration of 0.5 μg of α-, β-, γ-endorphin and DTγE on plasma prolactin. The animals were decapitated 30 min after injection.

	Plasma PRL (ng/ml)
Saline (1 μl)	26 ± 3
α-Endorphin (0.5 μg)	40 ± 7
β-Endorphin (0.5 μg)	143 ± 31**
γ-Endorphin (0.5 μg)	41 ± 9
DTγE (0.5 μg)	23 ± 3

(C) The effect of the intravenous administration of naloxone, DTγE and DEγE on plasma prolactin. The rats were killed 20 min after injection

	Plasma PRL (ng/ml)
Saline (0.5 ml)	65 ± 9
Naloxone (200 μg)	11 ± 2***
DTγE (50 μg)	37 ± 6*
DEγE (50 μg)	32 ± 4**

* $P < 0.05$ vs controls.
** $P < 0.005$ vs control.
*** $P < 0.001$ vs control.
6–9 animals per group.

Thereafter the possible interrelations between the effect of DEγE and dopaminergic systems on plasma levels of prolactin were investigated. Firstly, rats were injected with either saline of DEγE (50 μg subcutaneously) and after 60 min with saline or apomorphine (25 or 125 μg/kg subcutaneously). Plasma concentrations of prolactin, assessed at 20 min after the second injection, showed that only the large dose of apomorphine suppressed plasma prolactin levels in the saline-pretreated rats (Table 2). Again a stimulation of plasma prolactin levels was seen in rats pretreated with DEγE. This stimulation was suppressed by both doses of apomorphine. Thus, the increase of prolactin levels following DEγE administration could be counteracted by small doses of apomorphine. Secondly, sensitivity to apomorphine was tested in

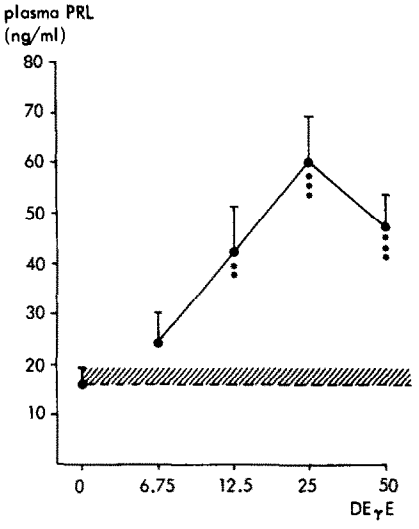

Fig. 1. The effect of the subcutaneous administration of four different doses (μg) of des-enkephalin-γ-endorphin (DEγE) on plasma concentration of prolactin 80 min after the injection. The mean of 6–7 animals per treatment group was plotted vs the dose of DEγE. Vertical bars indicate SEM. *Different from placebo treated controls (**$P < 0.025$, ***$P < 0.005$).

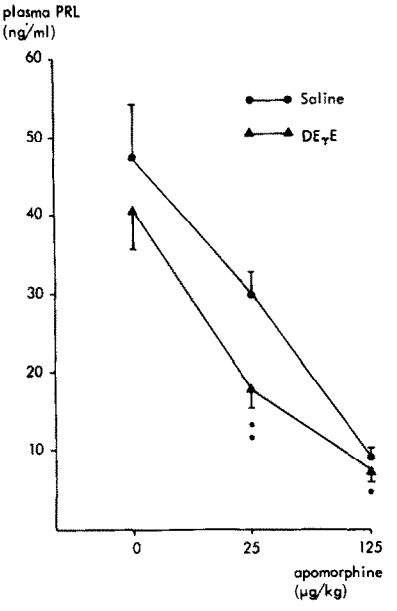

Fig. 2. The effect of subchronic administration of des-enkephalin-γ-endorphin (DEγE) on the sensitivity of prolactin secretion to apomorphine. Rats were pretreated for 4 days with either DEγE (10 μg subcutaneously twice a day) or with saline. 17 hr after the last injection, apomorphine (25 or 125 μg/kg) was injected subcutaneously and prolactin was measured after 20 min. The mean of 16–18 animals per treatment group was plotted vs the dose of apomorphine. Vertical bars indicate SEM. *Different from placebo, apomorphine treated animals (*$P < 0.05$, **$P < 0.005$).

rats subchronically treated with DEγE. It was found that administration of DEγE for 4 days (10 μg subcutaneously twice a day) increased the sensitivity to the inhibitory action of apomorphine (Fig. 2). Thus, 17 hr after the last peptide injection, the effect of 25 as well as 125 μg/kg apomorphine on prolactin levels was more pronounced in the DEγE pretreated rats, than in the saline pretreated rats.

γ-Endorpin in a wide dose-range (25 nM–3.5 μM) did not directly influence release of prolactin by the pituitary gland and the dispersed cultured cells *in vitro* but a dose-dependent partial reversal of the dopamine-induced inhibition of prolactin secretion was observed (Fig. 3; Table 3A; Table 5A). Naloxone (500 nM) did not have a direct effect on prolactin release, but it prevented the γ-endorphin-induced reversal of the dopamine-induced inhibition of prolactin secretion (Table 3B).

Table 2. The influence of apomorphine on prolactin secretion in animals pretreated with DEγE

t_0	t_{60}	Plasma PRL (ng/ml)
Saline	Saline	24 ± 3
Saline	APO (25 μg)	28 ± 5
Saline	APO (125 μg)	6 ± 1††
DEγE	Saline	42 ± 6†
DEγE	APO (25 μg)	21 ± 4*
DEγE	APO (125 μg)	6 ± 1**

Groups of male rats ($n = 10$) were injected at zero time with saline or DEγE (50 μg subcutaneously) and at 60 min with saline or apomorphine (25 or 125 μg/kg subcutaneously). They were decapitated at 80 min and plasma prolactin levels were measured.

* Different from DEγE–saline treatment (*$P < 0.01$, **$P < 0.001$).

† Different from saline–saline treatment (†$P < 0.02$, ††$P < 0.001$).

Both DTγE (10 nM–10 μM) and DEγE (100 nM, 1 μM) did not have a direct effect on prolactin release *in vitro* and did not interfere with the dopamine-induced inhibition of prolactin secretion (Tables 4 and 5). The experiments with DTγE and DEγE were also carried out in incubation media containing bacitracine (0.1 μM) and bovine serum albumin (0.1 μM) in order to prevent degradation of the peptides, as suggested by Enjalbert, Ruberg, Arancibia, Priam and Kordon (1979). Again, neither a direct effect of these peptides on prolactin secretion, nor an effect on the dopamine-induced inhibition of prolactin secretion, were seen (data not shown).

DISCUSSION

Exogenous and endogenous opioids have been shown to stimulate prolactin secretion *in vivo* (Rivier, Vale, Ling, Brown and Guillemin, 1977; Tolis, Hickley and Guyda, 1975; Dupont, Cusan, Labrie, Coy and Li, 1977; Rivier, Brown and Vale, 1977; Chihara,

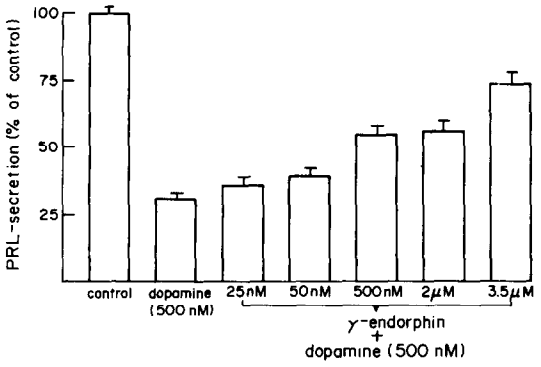

Fig. 3. Partial antagonism by various concentrations of γ-endorphin of the dopamine-induced inhibition of prolactin secretion by rat pituitary glands *in vitro*. The effects of dopamine were significantly blocked by 500 nM, 2 μM and 3.5 μM of γ-endorphin ($P < 0.01$, $P < 0.01$, $P < 0.01$).

Arimura, Coy and Schally, 1978). This effect on prolactin secretion can be blocked by specific opiate receptor antagonists, such as naloxone and naltrexone. Morphine, β-endorphin, α-endorphin and methionine-enkephalin do not have a direct action on prolactin release by the anterior pituitary glands *in vitro* (Shaar, Frederickson, Dininger and Jackson, 1977) or dispersed pituitary cells (Rivier *et al.*, 1973). Observations that met-enkephalin, β-endorphin and morphine block dopamine-mediated inhibition of prolactin secretion by the pituitary gland *in vitro* (Enjalbert *et al.*, 1979; Enjalbert, Ruberg, Fiore, Aranubia, Priam and Kordon, 1979), could not be confirmed by others (Muraki and Tokunaga, 1978; Login and MacLeod, 1979). The mechanism by which these opioid peptides elevate serum concentration of prolactin probably involves inhibition of the release of dopamine by tuberoinfundibular neurones into hypophyseal portal blood. The administration of morphine, β-endorphin and a synthetic enkephalin-analogue to rats resulted in a 85–95% reduction in the concentration of dopamine in the stalk plasma, and this effect could be prevented by naloxone (Gudelsky and Porter, 1979). In addition, it has been shown that dopamine turnover in the median eminence is suppressed by several opioid peptides (Ferland, Fuxe, Eneroth, Gustafsson and Skett, 1976; Deyo, Swift and Miller, 1979; Van Vugt, Bruni, Sylvester, Chen, Jeiri and Meites, 1979; Van Loon, De Souza and Shin, 1979). The results presented in this study are in agreement with these observations, in that β-endorphin stimulated release of prolactin and naloxone inhibited stress-induced prolactin secretion.

The peptides derived from β-lipotropin and beginning at amino acid 61 (tyrosine) have been shown to mimic most actions of morphine both *in vivo* and *in vitro* (Van Ree, De Wied, Bradbury, Hulme, Smyth and Snell, 1976; Graf, Szekely, Ronai, Dunai-Kovacs and Bajusz, 1976; Lord, Waterfield, Hughes and Kosterlitz, 1976). With regard to their behavioural effects, however, β-endorphin fragments exert highly specific effects in certain types of behavioural tests. β-Endorphin, α-endorphin and met-enkephalin delay the extinction of pole-jumping avoidance behaviour in rats, whereas γ-endorphin, which differs from α-endorphin by one additional amino acid, facilitates extinction of pole jumping avoidance behaviour (De Wied *et al.*, 1978a; De Wied, Bohus, Van Ree and Urban, 1978b; Le Moal, Koob and Bloom, 1979). This opposite effect was also found on passive avoidance behaviour (De Wied *et al.*, 1978a and b). In addition, γ-endorphin, but not morphine, β- and α-endorphin had a positive effect in various grip tests, comparable with that of haloperidol (De Wied *et al.*, 1978a). The

Table 3. The effects of γ-endorphin and naloxone on basal and dopamine-induced inhibition of prolactin secretion by normal rat pituitary glands *in vitro*

		PRL secreted into the medium (μg/mg pituitary gland)
(A)	Control	4.63 ± 0.36
	Dopamine (500 nM)	1.48 ± 0.25*
	γ-Endorphin (25 nM)	5.00 ± 0.31
	Dopamine (500 nM) + γ-endorphin (25 nM)	1.73 ± 0.15*
	γ-Endorphin (500 nM)	5.05 ± 0.26
	Dopamine (500 nM) + γ-endorphin (500 nM)	2.63 ± 0.28*†
(B)	Control	4.07 ± 0.27
	Dopamine (500 nM)	1.13 ± 0.12*
	γ-Endorphin (350 nM)	3.98 ± 0.33
	Naloxone (500 nM)	4.24 ± 0.30
	Dopamine (500 nM) + γ-endorphin (350 nM)	2.08 ± 0.36*†
	Dopamine (500 nM) + γ-endorphin (350 nM) + naloxone (500 nM)	1.34 ± 0.30*

Two different experiments (A and B) were performed.
Incubation time 5 hr; four flasks per group; data are given as mean ± SEM.
* $P < 0.01$ vs controls.
† $P < 0.01$ vs dopamine alone.

Table 4. The effects of DTγE and DEγE on basal and dopamine-induced inhibition of prolactin secretion by normal rat pituitary glands *in vitro*

		PRL secreted into the medium (μg/mg pituitary gland)
(A)	Control	7.76 ± 0.96
	DTγE 10 nM	8.02 ± 0.88
	DTγE 100 nM	7.48 ± 0.45
	DTγE 1 μM	8.16 ± 0.83
	DTγE 10 μM	8.32 ± 0.87
(B)	Control	7.36 ± 0.64
	Dopamine (500 nM)	4.02 ± 0.32*
	Dopamine (500 nM) + DTγE (100 nM)	4.20 ± 0.34*
	Dopamine (500 nM) + DTγE (1 μM)	3.96 ± 0.16*
	Dopamine (500 nM) + DTγE (10 μM)	4.16 ± 0.20*
(C)	Control	6.66 ± 0.06
	DEγE (100 nM)	6.43 ± 0.21
	DEγE (1 μM)	6.72 ± 0.29
(D)	Control	3.08 ± 0.37
	Dopamine (500 nM)	1.60 ± 0.16*
	Dopamine (500 nM) + DEγE (1 nM)	1.58 ± 0.26*
	Dopamine (500 nM) + DEγE (10 nM)	1.72 ± 0.40*
	Dopamine (500 nM) + DEγE (100 nM)	1.30 ± 0.14*
	Dopamine (500 nM) + DEγE (1 μM)	1.80 ± 0.40*

Four different experiments (A, B, C and D) were performed.
Incubation time 5 hr; four flasks per group; data are given as mean ± SEM.
* $P < 0.01$ vs control.

effects of γ-endorphin were apparently not dependent on opiate receptor activation since the removal of the N-terminal amino acid residue tyrosine, which eliminates opiate-like activity, enhanced the influence of γ-endorphin on active and passive avoidance behaviour and in the grip tests (De Wied *et al.*, 1978a). Further studies indicated that the pharmacological profile of DTγE (βE 2–17) in various aspects resembled that of the neuroleptic drug haloperidol (De Wied *et al.*, 1978a; Van Ree, Bohus and De Wied, 1980b; Dorsa, Van Ree and De Wied, 1979), although it could not be regarded as a classical neuroleptic compound (De Wied *et al.*, 1978a; Van Ree, Witter and Leysen, 1978). In view of these findings, it was postulated that DTγE or a closely related neuropeptide might be an endogenous peptide with neuroleptic-like activity with a profile more specific than that of currently used neuroleptic drugs (De Wied, 1978). Further investigations revealed that DEγE is the shortest sequence of various fragments of γ-endorphin that showed potencies comparable with that of DTγE in two grip tests and on extinction of pole jumping

Table 5. The effect of γ-endorphin, DTγE and DEγE on basal and dopamine-induced inhibition of prolactin secretion by normal cultured pituitary cells

		PRL secreted into the medium (ng/dish)
(A)	Control	156 ± 8
	Dopamine (500 nM)	86 ± 5*
	γ-Endorphin (350 nM)	161 ± 19
	Dopamine (500 nM) + γ-endorphin (350 nM)	128 ± 6**
(B)	Control	711 ± 27
	Dopamine (500 nM)	313 ± 35*
	DTγE (1 μM)	775 ± 19
	Dopamine (500 nM) + DTγE (1 μM)	254 ± 24*
	DEγE (1 μM)	627 ± 21
	Dopamine (500 nM) + DEγE (1 μM)	250 ± 9*

Two different experiments (A and B) were performed.
Incubation time 4 hr; 5 dishes per group; data are given as mean ± SEM.
* $P < 0.01$ vs controls.
** $P < 0.01$ vs dopamine alone.

avoidance behaviour, which were used to measure neuroleptic-like activity (De Wied *et al.*, 1980). These observations in animals stimulated clinical trials in which the proposed antipsychotic action of γ-type endorphins was tested. It was found that both DTγE and DEγE decreased symptomatology in a number of patients suffering from schizophrenic psychosis (Verhoeven *et al.*, 1979; Van Ree *et al.*, 1980a, Emrich, Zaudig, Kissling, Dirlich, Von Zerssen and Herz, 1980).

In the present study it was shown that the actions of these neuroleptic-like peptides (γ-endorphin, DTγE and DEγE) on prolactin secretion differ from those of the more classical drugs like haloperidol. γ-Endorphin stimulated prolactin release *in vivo* and antagonized in a dose-dependent way, the dopamine-mediated inhibition of prolactin release by the pituitary gland *in vitro*. This latter effect of γ-endorphin is comparable with that of several neuroleptic drugs like haloperidol, pimozide and perphenazine (MacLeod, 1976; MacLeod and Lehmeyer, 1974). Apart from these dopamine-receptor antagonists, however, several other substances like thyrotropin releasing hormone (TRH) and dibutyryl-cAMP have also been shown to reverse the dopamine-effect on prolactin release by the pituitary gland *in vitro* in a dose-dependent manner (MacLeod, 1976; Hill-Samli and MacLeod, 1974). This effect of γ-endorphin is probably an opioid effect because it was prevented by naloxone. That the effects of γ-endorphin can be antagonized by both dopamine and naloxone was recently also found in a behavioural model. Kirally, Tapfer, Borsy and Gráf (1981) reported that γ-endorphin inhibited the amphetamine-induced stereotypy in rats, and that this anti-amphetamine effect of γ-endorphin could be antagonized to a certain extent by the dopamine receptor stimulant bromocriptine, as well as by naloxone.

The pharmacological profile of DTγE and DEγE resembles that of classical neuroleptic drugs in several ways (Van Ree *et al.*, 1980b), but DTγE has no affinity for neuroleptic or apomorphine binding sites *in vitro*, nor does it significantly affect opiate-receptor binding (Van Ree *et al.*, 1980b; Van Ree *et al.*, 1978; Pedigo, Ling, Reisine and Yamamura, 1979a), although the peptide seems to interfere with spiperone binding *in vivo* (Pedigo, Schallert, Overstreet, Ling, Ragan, Reisine and Yamamura, 1979b). The basically different action of DTγE and DEγE from that of the known neuroleptic drugs was also shown in the present study. No direct effect of DTγE and DEγE on prolactin release *in vitro* by the pituitary gland was observed, while intravenous administration of these peptides suppressed the stress-induced plasma prolactin release and prolactin release was stimulated when prolactin control levels were low. Recent data on behavioural effects of γ-type endorphins and their interrelations with the effect of apomorphine suggest that DTγE and DEγE act as dopamine antagonists selectively on those dopamine receptor systems, which are stimulated by small doses of apomorphine and which may be located presynaptically in mesolimbic dopaminergic pathways (Van Ree, Innemee, Louwerens, Kahn and De Wied, 1982a; Van Ree, Caffé and Wolterink, 1982b). Subchronic treatment with DEγE for 4 days resulted in an enhanced sensitivity to the behavioural effects of small doses of apomorphine, suggesting that these receptor systems have become supersensitive. It has been argued that at least part of the dopaminergic receptor systems present on prolactin releasing cells in the pituitary bear similarities with those located presynaptically in mesolimbic dopaminergic systems (Meltzer and Simonovic, 1981). A similar action of γ-type endorphins on these dopamine receptor systems in the pituitary, if they are present, could explain the findings that DEγE increased basal prolactin secretion and that subchronic treatment with this peptide leads to an enhanced sensitivity to apomorphine with respect to its decreasing effect on prolactin release. It is puzzling, however, that this peptide does not interfere with the dopamine-induced inhibition of prolactin release *in vitro*, although it must be borne in mind that the influence of γ-type endorphins could not be demonstrated due to the *in vitro* conditions used. Moreover, the inhibition of stress-induced prolactin release by γ-type endorphins complicates the picture. This effect might be due to a suprahypophyseal action of these peptides, in which dopamine or other neurotransmitter systems are involved, eventually leading to an increase in the amount of dopamine reaching the pituitary lactotroph via the portal stalk blood and consequently in a decreased prolactin release. In conclusion, the present data suggest that γ-endorphin stimulates prolactin release by a direct effect on the pituitary and that the γ-endorphin fragments DTγE and DEγE can stimulate or attenuate prolactin release depending on the activity of the systems involved in prolactin secretion, suggesting that these peptides may function as modulators of ongoing activity in these systems.

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