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Delayed Activation of Tuberoinfundibular Dopamine Neurons and Suppression of Prolactin Secretion in the Rat after Morphine Administration[1]

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ABSTRACT

The effect of morphine administration on the subsequent stimulation of prolactin (PRL) secretion and the release of dopamine from tuberoinfundibular neurons was examined in this study. The administration of morphine (15 mg/kg s.c.) resulted 4 hr later in suppressed serum PRL concentrations. In addition, the increase in serum PRL concentrations induced by restraint stress was attenuated greatly in rats treated 4 hr earlier with morphine. The morphine-induced attenuation of the PRL response to restraint stress was time-dependent and dose-related. The suppressive effect of morphine on PRL secretion was observed 3 to 6 hr after its administration and at doses of 10 to 20 mg/kg. A single injection of morphine also resulted 4 hr later in an attenuation of the PRL response to a second injection of morphine (7.5 mg/kg); however, the increase in serum PRL concentration produced by α-methyltyrosine (250 mg/kg) was unaltered by prior morphine administration. The suppressive effect of morphine on PRL secretion was not observed in rats treated with the opiate antagonist naloxone (2.5 mg/kg). Associated with the delayed suppressive effect of morphine on serum PRL concentratins was a delayed increase in the concentration of dopamine in hypophysial portal plasma and an increase in the turnover of dopamine in the median eminence. The morphine-induced stimulation of the release of dopamine into hypophyseal portal blood was attenuated significantly in animals treated with naltrexone (1 mg/kg). It is concluded that morphine exerts a biphasic effect on both the secretion of PRL and the release of dopamine from tuberoinfundibular neurons. In contrast to the acute effect of morphine to suppress the release of dopamine from tuberoinfundibular neurons and enhance the secretion of PRL, morphine exerts a delayed effect to stimulate the release of dopamine from these hypothalamic neurons and inhibit PRL secretion.

The presence of opiate-like peptides in the arcuate nucleus and median eminence regions of the hypothalamus (Bloom *et al.*, 1978; Sar *et al.*, 1978) is supportive of the view that endorphins and/or enkephalins have a role in the regulation of pituitary gland function. Indeed, the systemic or intraventricular administration of endogenous opiate-like peptides, as well as morphine, results in an increase in the serum concentration of PRL (Bruni *et al.*, 1977; Ojeda et al., 1974; Rivier *et al.*, 1977; Cusan *et al.*, 1977).

The secretion of PRL from the anterior pituitary gland is believed to be inhibited tonically through neuronal mechanisms in the hypothalamus. Dopamine released from tuberoinfundibular neurons into hypophysial portal blood may act directly on the lactotroph to effect this inhibition (MacLeod, 1976; Gudelsky, 1981).

Thus, the stimulatory effect of morphine on PRL secretion is thought to result, in part, from a removal of the inhibitory dopaminergic control of PRL secretion. This contention is based on the findings that morphine and opioid peptides acutely reduce the turnover and synthesis of dopamine in the median eminence (Ferland *et al.*, 1977; Van Vugt *et al.*, 1979; Van Loon *et al.*, 1980; Alper *et al.*, 1980) and suppress the secretion of dopamine from tuberoinfundibular neurons into hypophysial portal blood (Gudelsky and Porter, 1979; Haskins *et al.*, 1981; Reymond *et al.*, 1983).

Morphine also has been shown to have a delayed effect to suppress the secretion of PRL. In a preliminary communication, Grandison (1982) showed that 4 hr after the administration of morphine the stimulation of PRL secretion induced by a second injection of morphine or 5-hydroxytryptophan was attenuated greatly. The present study was undertaken in order to characterize more fully the delayed inhibitory effect of morphine on PRL secretion and to determine whether this effect of morphine also is associated with an altered release of dopamine from tuberoinfundibular neurons.

Materials and Methods

Animals. Adult male rats (175–250 g) of the Sprague-Dawley strain (Sprague-Dawley, Inc., Madison, WI) were used in these experiments.

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ABBREVIATIONS: PRL, prolactin; α-MT, α-methyltyrosine.

The animals were maintained in an air-conditioned and light controlled (light on 7:00 A.M.–7:00 P.M.) room. The animals had free access to food and water.

Dopamine turnover. The turnover of dopamine in the median eminence was assessed from the α-MT-induced decline of dopamine concentrations as described previously (Gudelsky and Moore, 1977). Briefly, rats were injected with morphine (15 mg/kg s.c.) or the solvent vehicle 3.5 hr before the administration of α-MT (250 mg/kg i.p.). The animals were killed by decapitation 1 hr after the injection of α-MT. Zero-time control rats were given 0.15 M NaCl instead of α-MT. The median eminence was dissected from the rest of the rat brain and homogenized in 150 μl of 0.3 N perchloric acid. The tissue homogenate was centrifuged at 10,000 × *g* for 1 min. The dopamine content of the resulting supernatant fluid was quantified using high-pressure liquid chromatography with electrochemical detection. Protein in the pellet was measured according to Lowry *et al.* (1951).

Collection of hyphopysial portal blood. Pituitary stalk blood was collected for 45 min from pentobarbital-anesthetized rats as described previously (Gudelsky and Porter, 1979). Dopamine was measured in the plasma samples by radioenzymatic assay.

PRL studies. The experiments were designed such that the rats were injected s.c. with morphine (15 mg/kg) or the solvent vehicle 4 hr before their exposure to one of the following: restraint stress (placement of the rats in ventilated plastic holding boxes), morphine (7.5 mg/kg s.c.), the solvent vehicle or α-MT (250 mg/kg i.p.). The rats were killed by decapitation 5 min after the initiation of the stress, 30 min after the second injection of morphine or the solvent vehicle or 60 min after α-MT. In other experiments designed to antagonize the inhibitory effect of morphine on restraint stress-induced release of PRL, rats received naloxone (2.5 mg/kg s.c.) or apomorphine (1 mg/kg s.c.) 5 min before morphine administration.

Hormone determinations. PRL was measured in serum from trunk blood by radioimmunoassay according to the procedures outlined by the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases. Serum PRL values are expressed in terms of National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases rat PRL-RP-2. The sensitivity of the assay was 1 ng/ml. The interassay and intraassay coefficients of variance were 10 and 4%, respectively.

Drugs. Morphine sulfate was obtained from the National Institute of Drug Abuse (Bethesda, MD). Apomorphine was purchased from Mallinckrodt (St. Louis, MO). Naloxone and naltrexone were generously provided by Endo Laboratories, Inc. (Garden City, N.Y.) α-MT was purchased from Sigma Chemical Co. (St. Louis, MO.).

Statistical analysis. The data were evaluated statistically utilizing an analysis of variance followed by the Newman-Keules test (Sokal and Rohlf, 1969). Student's *t* test was used in some instances.

Results

In agreement with previous reports, morphine (15 mg/kg s.c.) produced an initial rapid elevation of serum PRL concentrations (data not shown). However, serum PRL concentrations were significantly reduced 4 hr after the administration of this dose of morphine when compared to serum PRL concentrations in vehicle-treated animals (4 ± 1 *vs.* 12 ± 6 ng/ml, respectively) (fig. 1).

Restraint stress (5 min) and morphine (7.5 mg/kg s.c.) also caused a rapid and marked increase in serum PRL concentrations (fig. 1). However, the PRL responses to stress or morphine in animals treated with morphine (15 mg/kg) 4 hr earlier were only 25 to 50% of those in vehicle-pretreated rats. In contrast, the α-MT (250 mg/kg i.p.)-induced elevation of serum PRL concentrations was similar in vehicle- and morphine-pretreated animals.

The dose-response relationship for the morphine-induced suppression of the stress-induced increase in serum PRL concentrations is shown in figure 2. Morphine attenuated the PRL response to restraint stress at doses of 5 to 20 mg/kg. A maximal inhibitory effect was observed after 15 mg/kg of morphine.

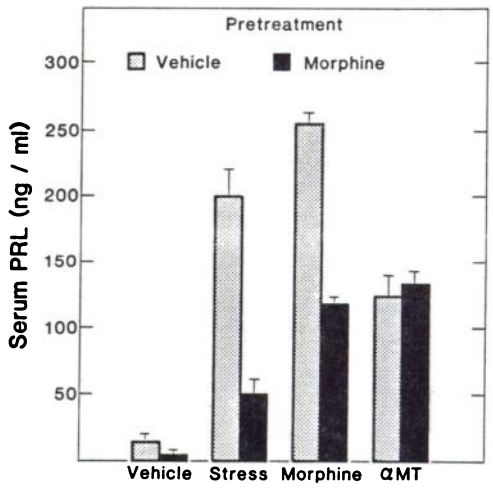

Fig. 1. Effect of morphine treatment on the subsequent stimulation of PRL secretion. Rats were given morphine (15 mg/kg s.c.) or the solvent vehicle 4 hr before restraint stress, morphine (7.5 mg/kg s.c.), α-MT (250 mg/kg i.p.) or 0.15 M NaCl (vehicle). The animals were killed after 5 min of stress, 30 min after morphine or the vehicle and 60 min after α-MT. Column heights and vertical lines represent the means and S.E.s, respectively, of six to eight animals.

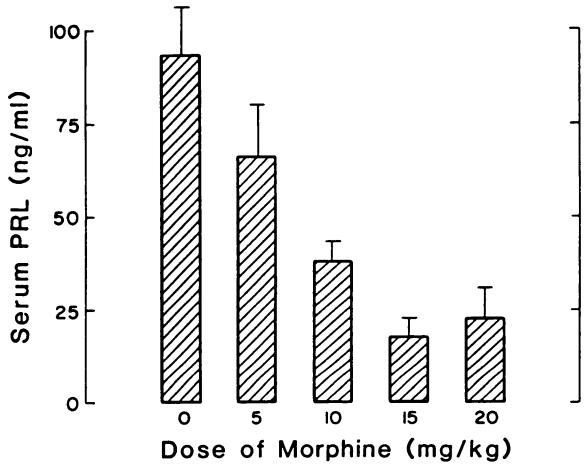

Fig. 2. Dose-response relationship for morphine-induced suppression of PRL secretion. Rats were given morphine or the solvent vehicle s.c. 4 hr before restraint stress. The animals were killed after being subjected to 5 min of restraint stress. Column heights and vertical lines represent the means and S.E.s, respectively, of six rats.

A significant inhibitory effect of morphine on the stress-induced release of PRL was observed 3 to 6 hr after its administration (fig. 3). No significant influence of morphine on the PRL response to stress was observed 2 hr after opiate administration. Interestingly, 8 hr after morphine administration the stress-induced increase in serum PRL concentrations was significantly ($P < .05$) greater than in vehicle-treated rats.

The treatment of rats with naloxone (2.5 mg/kg s.c.) effectively prevented the delayed inhibitory effect of morphine on the restraint stress-induced rise in serum PRL concentrations (fig. 4). The PRL response to restraint stress in rats given naloxone and morphine was not significantly different from that in vehicle-treated animals and was significantly ($P < .01$) greater than that in animals treated only with morphine. Naloxone treatment alone had no significant effect on the PRL

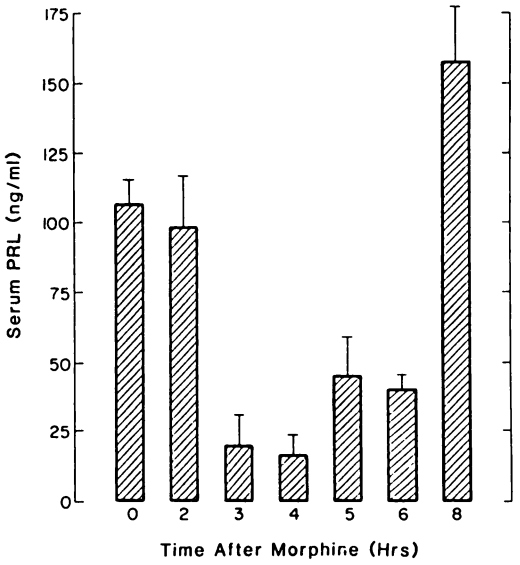

Fig. 3. Time course for the morphine-induced inhibition of PRL secretion. Rats were injected with morphine (15 mg/kg s.c.) or the solvent vehicle at various times before the initiation of 5 min of restraint stress. Column heights and vertical lines represent means and S.E.s, respectively, for six rats.

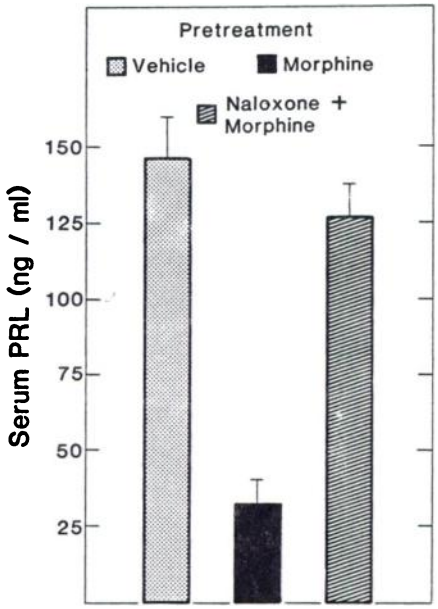

Fig. 4. Effect of naloxone on the stress-induced release of PRL in morphine-treated rats. Rats were given morphine (15 mg/kg s.c.) or the solvent vehicle 4 hr before 5 min of restraint stress. Some animals received naloxone (2.5 mg/kg s.c.) 5 min before the administration of morphine. Serum PRL concentrations in untreated, nonstressed rats were 11 ± 4 ng/ml. Column heights and vertical lines represent means ± S.E.s, respectively, for 8 to 10 animals.

response to restraint stress 4 hr after its administration (data not shown).

The delayed (4 hr) effect of morphine on the release of dopamine from tuberoinfundibular neurons was evaluated by measuring the concentration of dopamine in hypophysial portal plasma (fig. 5). Dopamine concentrations in portal plasma of rats treated with morphine (15 mg/kg s.c.) 4 hr before the collection of pituitary stalk blood were almost 3 times those in the control rats (1.3 ± 0.13 *vs.* 0.5 ± 0.06 ng/ml). The morphine-induced elevation of the concentration of dopamine in pituitary

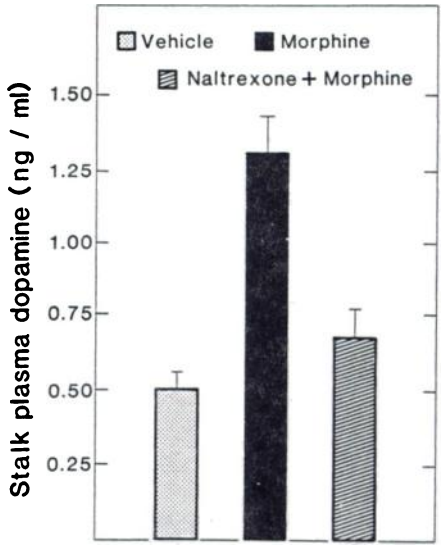

Fig. 5. Morphine-induced elevation of dopamine concentrations in hypophysial plasma. Hypophysial portal blood was collected from rats 4 hr after the administration of morphine (15 mg/kg s.c.) or its solvent vehicle. Some rats were given naltrexone (1 mg/kg s.c.) 15 min before morphine administration. The column heights and vertical lines represent the mean ± S.E. of six to nine rats.

TABLE 1

Effect of morphine on the α-MT-induced decline of dopamine concentrations in the median eminence

Rats received morphine (15 mg/kg s.c.) or the solvent vehicle 4.5 hr before decapitation. One hour before decapitation half of the animals in each group received the vehicle and half were injected with α-MT (250 mg/kg i.p.). Values represent the mean ±S.E. for 9 to 11 rats.

Pretreatment	Treatment	
	Vehicle	α-MT
	ng dopamine/mg protein	
Vehicle	142 ± 4	90 ± 3
Morphine	147 ± 8	62 ± 4*

* $P < .05$ when compared to the value for the vehicle-pretreated group.

stalk plasma was antagonized completely in rats pretreated with naltrexone (1 mg/kg s.c.) (fig. 5). The concentration of dopamine in pituitary stalk plasma of rats given naltrexone and morphine was significantly ($P < .01$) less than that in rats given only morphine and did not differ significantly from that in the vehicle-treated controls.

The effect of morphine on the α-MT-induced decline of dopamine concentrations in the median eminence, which was used as an index of dopamine turnover, is presented in table 1. Treatment of rats with morphine (15 mg/kg s.c.) had no effect on the steady-state concentration of dopamine in the median eminence. However, 4 hr after morphine treatment the α-MT-induced decline of the dopamine concentration in the median eminence was significantly ($P < .05$) greater than that in the control animals. One hour after α-MT administration there was a 37% reduction in the concentration of dopamine in the median eminence of control rats, whereas a 58% reduction was observed in morphine-treated rats.

It was of further interest to consider the hypothesis that the late-occurring suppression of PRL secretion after morphine administration was due to the inhibitory feedback effect of the initial increase in serum PRL concentrations, as PRL has been shown to inhibit its own secretion by increasing the release of dopamine from tuberoinfundibular neurons (Gudelsky *et al.*,

1976; Gudelsky and Porter, 1980). In order to test this hypothesis, the PRL response to stress was evaluated in rats given apomorphine to suppress the initial morphine-induced rise in serum PRL concentrations. In a preliminary experiment, it was found that apomorphine (1 mg/kg) prevented the acute morphine-induced increase in serum PRL concentrations completely; yet the PRL response to stress was unaltered 4 hr after apomorphine administration (data not shown). Nevertheless, apomorphine treatment failed to alter the delayed effect of morphine to suppress the PRL response (fig. 6). Serum PRL concentrations in stressed rats treated previously with apomorphine and morphine were 34 ± 10 ng/ml, whereas the values for animals given morphine alone were 43 ± 12 ng/ml. PRL levels in untreated stressed rats were 156 ± ng/ml.

Discussion

In the present study, it was found that 3 to 6 hr after a single injection of morphine there was a dose-dependent suppression of the subsequent stimulation of PRL secretion induced by restraint stress or a second injection of morphine. The development of this delayed inhibitory effect of morphine on PRL secretion is in accord with the preliminary findings of Grandison (1982) who found that the PRL responses to morphine, stress or 5-hydroxytryptophan were diminished in animals given morphine 4 hr earlier. In the present study it also was found that basal serum concentrations of PRL were reduced 4 hr after the administration of morphine.

It should be noted that, although the PRL responses to morphine or stress in morphine pretreated rats were much less than those in control animals in terms of absolute nanograms per milliliter of PRL, the magnitude of the elevations of serum PRL concentrations in morphine- and vehicle-pretreated animals was similar when calculated in terms of percentage of the respective base-line serum concentrations of PRL. This is due to the lower basal serum PRL concentrations in morphine-pretreated animals compared to the controls. Nevertheless, from the standpoint of pituitary gland function it would seem that a difference of less than 10 ng/ml in basal serum PRL concentrations in control and morphine-treated rats is negligible compared to the difference of almost 150 ng/ml in the elevations of serum PRL produced by a second injection of morphine or stress in these two groups.

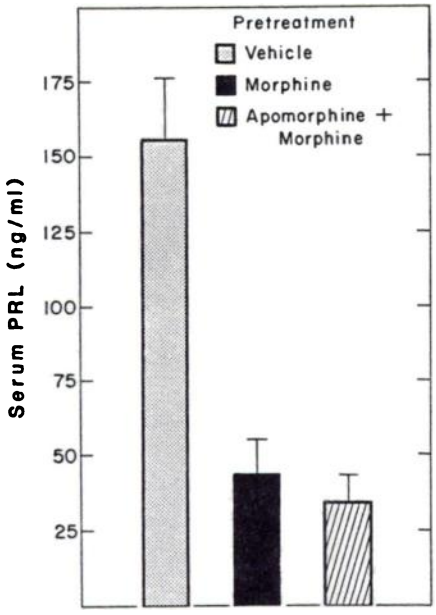

Fig. 6. Effect of apomorphine on the stress induced release of PRL in morphine-treated rats. Rats were given morphine (15 mg/kg s.c.) or the solvent vehicle 4 hr before 5 min of restraint stress. Some animals received apomorphine (1 mg/kg s.c.) 5 min before the administration of morphine. Serum PRL concentrations in untreated, nonstressed rats were 17 ± 6 ng/ml. Column heights and vertical lines represent means and S.E.s, respectively, of six animals.

It is unlikely that the suppressed PRL responses to stress and morphine in morphine-treated animals are the result of a diminished store of releasable PRL in the anterior pituitary gland because the PRL response to α-MT was similar in vehicle- and morphine-treated rats. Additionally, there was a normal PRL response to stress 2 hr after morphine administration, whereas the response was blunted 4 hr after opiate treatment. If releasable stores of pituitary PRL were depleted by morphine, then it would be expected that the stress response also would be attenuated 2 hr after morphine treatment, and this was found not to be the case. Grandison (1982) also observed that the spontaneous and thyrotropin releasing hormone-induced release of PRL *in vitro* were similar from pituitary tissue of control and morphine-treated rats. This strengthens further the view that diminished stores of pituitary PRL are not responsible for the inhibitory effect of morphine on the subsequent stimulation of PRL secretion.

The delayed inhibitory effect of morphine on the subsequent stimulation of PRL secretion has been referred to by Grandison (1982) as "acute tolerance." However, it is not certain whether the delayed inhibitory effect of morphine on PRL secretion represents the development of classical tolerance involving opiate mechanisms or the development of some other type of adaptive mechanism concerned with hypothalamic-pituitary gland function.

The delayed inhibitory effect of morphine on PRL secretion is associated with an apparent stimulation of the activity of tuberoinfundibular neurons, as evidence by the increased secretion of dopamine into hypophysial portal blood and the increased turnover of dopamine in the median eminence. In view of the role of dopamine in the tonic inhibition of PRL secretion (Macleod, 1976), the delayed morphine-induced increase in the release of dopamine from tuberoinfundibular neurons may be part of the mechanism by which morphine exerts its delayed inhibitory effect on the secretion of PRL.

The delayed effect of morphine to stimulate the release of dopamine from tuberoinfundibular neurons is in dramatic contrast to the acute effect of morphine on these hypothalamic neurons. The systemic or iontophoretic administration of morphine has been shown to result in the immediate suppression of the release of dopamine from tuberoinfundibular neurons, as evidenced by a decrease in dopamine turnover in the median eminence (Ferland *et al.*, 1977; Van Vugt *et al*, 1979; Van Loon *et al.*, 1980; Alper *et al.*, 1980) and a reduction in the concentration of dopamine in hypophysial portal plasma (Gudelsky and Porter, 1979; Haskins *et al.*, 1981; Reymond *et al.*, 1983). Thus, a biphasic effect of morphine on the activity of tuberoinfundibular dopamine neurons appears to be involved in the stimulatory and inhibitory effects of morphine on PRL secretion. An initial morphine-induced suppression of the release of dopamine is associated with an increased secretion of PRL (Gudelsky and Porter, 1979; Haskins *et al.*, 1981) and, as shown in the present study, a delayed morphine-induced stimulation

of the release of dopamine is associated with a suppression of PRL secretion.

The mechanisms involved in the delayed morphine-induced activation of tuberoinfundibular dopamine neruons and subsequent suppression of PRL secretion remain unclear. As evidenced by the effects of naloxone and naltrexone to antagonize the delayed effects of morphine on the release of dopamine and PRL, some type of opiate receptor-mediated event appears to be involved. However, the delayed effect of morphine to enhance the release of dopamine from tuberoinfundibular neurons may be the result of a secondary event resulting from the interaction of the opiate with its receptor, in contrast to a primary action of morphine on these neurons, as appears to be the mechanism involved in the acute suppression of the release of dopamine from these hypothalamic neurons (Haskins *et al.*, 1981). For example, PRL itself has been shown to have a feedback effect to enhance the release of dopamine from these hypothalamic neurons (Hökfelt and Fuxe, 1972; Gudelsky *et al.*, 1976; Gudelsky and Porter, 1980; Foreman and Porter, 1981). In the present study, the possibility was considered that the initial elevation of serum PRL concentrations produced by morphine could elicit this feedback regulatory mechanism. However, in animals given apomorphine, the initial effect of morphine to elevate serum PRL concentrations was prevented completely whereas the delayed inhibitory effect of morphine on PRL secretion was still evident. Hence, this does not appear to be a plausible explanation.

Another explanation for the present findings is that the morphine-induced stimulation of the release of dopamine from tuberoinfundibular neurons is mediated by α-MSH. Greidanus *et al.* (1979) have reported that morphine treatment increases the plasma concentration of α-MSH in the rat. It is of interest that α-MSH has been shown to increase the concentration of dopamine in pituitary stalk plasma (Porter *et al.*, 1980) and increase the turnover of dopamine in the median eminence (Lichtensteiger and Monnet, 1979). Additionally, it has been shown that α-MSH suppresses serum PRL concentrations in the rat (Khorram *et al.*, 1982; Newman *et al.*, 1985). Hence, it can be hypothesized that morphine causes an initial inhibition of the release of dopamine from tuberoinfundibular neurons and a subsequent stimulation of the release of PRL, as well as α-MSH. This is then followed by an α-MSH-mediated stimulation of the release of dopamine from these neurons and, consequently, a suppression of PRL secretion.

Regardless of the mechanisms involved in the delayed effects of morphine on the secretion of dopamine and PRL, it is clear that morphine, and perhaps endogenous opioids, can serve as both facilitators and suppressors of the release of dopamine from the hypothalamus and, consequently, PRL from the anterior pituitary gland.

Acknowledgments

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