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The "low-dose" concept and the paradoxical effects of prolactin on grooming and sexual behavior

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Abstract

The effects of prolactin on animal behavior include the stimulation of novelty-induced grooming in rats. This effect has been demonstrated in hyperprolactinaemic animals bearing pituitary homografts under the kidney capsule or after intracerebroventricular (i.c.v.) administration of prolactin. Since plasma prolactin levels in hyperprolactinaemic rats are similar to those of animals injected with low doses of rat prolactin, we studied the effects of this hormone injected subcutaneously (s.c.) in a dose range of 5–50 μg/kg. Novelty-induced grooming was enhanced only in rats injected with 5 or 10 μg/kg rat prolactin, whereas no effect was observed after the s.c. injection of the higher dose. The sexual behavior of male rats is also affected by prolactin. Male rats with normal mating activity showed enhanced sexual behavior when injected s.c. with rat prolactin (5, 10 or 50 μg/kg). In animals with poor sexual performance or in impotent rats, prolactin (5 or 10 μg/kg, but not 50 μg/kg) restored the full pattern of sexual behavior. An increased lordosis quotient was also observed in ovariectomized rats treated with prolactin 5 or 10 μg/kg. These results suggest that, besides the duration of hyperprolactinaemia, the effective level of plasma prolactin is important for the expression of the behavioral effects of this hormone.

Keywords: Low dose; Prolactin; Grooming, Novelty-induced; Sexual behavior, Male; Sexual behavior, Female

1. The "low-dose" concept

The experiments described in this paper were not done during my stay at the Rudolf Magnus Institute for Pharmacology in Utrecht, between 1980 and 1982, but later. However, the "philosophy" inspiring all these studies comes undoubtedly from David De Wied, who taught me the basic elements of behavioral psychopharmacology.

My research field in that period was mainly related to prolactin and its behavioral effects (Drago, 1981). The model of pituitary homografts under the kidney capsule in rats, leading to prolonged hyperprolactinaemia, was used in those experiments. We found that sustained plasma prolactin levels were accompanied by behavioral changes, e.g. increased grooming of rats exposed to a novel environment (Drago et al., 1980). However, our early attempt to reproduce this behavioral change after intracerebroventricular (i.c.v.) injection of the hormone did not yield consistent results. After a series of preliminary and unsatisfactory experiments, I consulted Prof. De Wied. He listened in silence to my story, and finally advised me to try a "low-dose" of prolactin.

Indeed, the "low-dose" concept had already been introduced at the Rudolf Magnus Institute and referred to the amount of a substance that has a physiological meaning in terms of concentration and functional effects. The notion that neuropeptides can cross the blood–brain barrier when administered peripherally at low doses was introduced in the late 1970s (Greenberg et al., 1976; Landgraf et al., 1979; Kastin et al., 1979), and actually some of these substances (e.g. vasopressin, oxytocin and their analogues) were shown to exert central effects after subcutaneous (s.c.) injections of low doses. For example, the enhancement of acquisition and retention of avoidance behavior

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and of novelty-induced grooming occurs after i.c.v. or peripheral injection of low doses of oxytocin and vasopressin. These neuropeptides display an inverted U-shape dose–response curve for this effect (De Wied and Gispen, 1977; De Kloet and De Wied, 1980; Meisenberg, 1981; Caldwell et al., 1986; Drago et al., 1986a; Pedersen et al., 1988).

Of course, it was very easy to demonstrate that a "low-dose" of prolactin injected i.c.v. stimulates novelty-induced grooming of rats (Drago et al., 1980). Later, we found that, like adrenocorticotropic hormone (ACTH), prolactin exhibits an inverted U-shape curve of the stimulation of novelty-induced grooming and that the two hormones interact in this effect (Drago et al., 1983; Drago, 1988). Furthermore, the actual presence of small quantities of prolactin in the brain is essential for hyperprolactinaemia-induced excessive grooming in the rat. The i.c.v. injection of highly diluted (1:100) antiserum against rat prolactin totally suppresses hyperprolactinaemia-induced behavioral changes (Drago et al., 1986b).

Finally, we realized that the model of endogenous hyperprolactinaemia as induced by pituitary homografts mimics the increase in plasma prolactin levels following peripheral injection of the hormone in a "low dose" (Drago and Bohus, 1981). It should be noted that, depending on the number of glands implanted under the kidney capsule, pituitary homografts lead to plasma prolactin levels between 50 and 200 ng/ml, and in any case lower than 300 ng/ml (Bailey and Herbert, 1982; Drago et al., 1980; Drago and Bohus, 1981; Svare et al., 1979). In contrast, subjects with pituitary tumors may exhibit plasma prolactin levels higher than 1000 ng/ml (Thorner et al., 1974; Kalra et al., 1981; Weber et al., 1982). Thus, for more than a decade, and often under the supervision of De Wied, we used the model of pituitary homografts to study in detail the behavioral effects of prolactin in rats (Drago et al., 1981a, 1982a,b, 1985a,b, 1986b, 1990, 1992; Drago and Amir, 1984; Kovacs et al., 1984; Drago and Scapagnini, 1985; Drago and Bohus, 1986).

At the end of 1981, I submitted an abstract on hyperprolactinaemia-induced behavioral changes in rats to the International Society for Psychoneuroendocrinology Congress in Canada. Since at the last moment I was unable to attend the meeting, De Wied offered to present the data on my behalf, for which kindness I remain indebted to him.

2. The effect of low doses of prolactin on grooming behavior of male rats

We have recently replicated the experiments on grooming behavior using male rats of the Wistar strain (Charles River, weighing 150–170 g) injected s.c. with various doses of rat prolactin (Amersham, USA), i.e. 5, 10 or 50 μg/kg, dissolved in saline. Injections were made 1 h before grooming behavior was analyzed according to the original method described by Gispen et al. (1975). The rats were placed individually into Plexiglass boxes (24 × 12 × 24 cm) in a low-noise room. After a minute of adaptation, the behavior of the rats was sampled every 15 s, and the occurrence of grooming was recorded during a 30-min session. Grooming behavior of all animals was recorded on a tape using a videocamera, and then scored on a monitor display by two independent observers. As with the experiments performed at the Rudolf Magnus Institute in Utrecht, I preferred that somebody else injected the animals with prolactin, but I was usually one of the two observers.

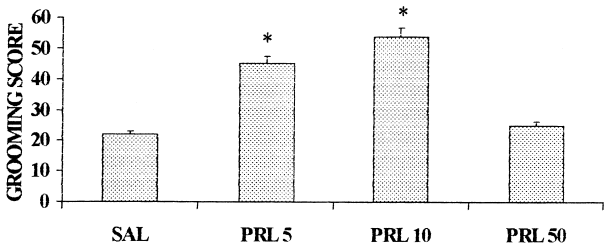

Fig. 1. Effects of rat prolactin on novelty-induced grooming of rats. Values are means ± S.E.M. Each experimental group consisted of seven animals. Prolactin (5, 10 or 50 μg/kg) was injected s.c. 1 h prior to 30-min behavioral testing. For the procedure of behavioral test, see text. * Significantly different as compared to saline-injected animals ($P < 0.05$, Dunnett's test for multiple comparisons).

As compared to saline, s.c. injected prolactin increased the grooming activity of male rats, but a dose of 50 μg/kg was ineffective in this respect (Fig. 1). Interestingly, the potency of 5 and 10 μg/kg doses was similar to that found in other experiments with low doses of prolactin injected i.c.v. (Drago et al., 1983).

3. The paradoxical stimulation of male sexual behavior by prolactin

A great number of animal and human studies have been carried out to analyze the effects of prolactin on sexual behavior. The main reason for this a great interest is the apparent relationship between hyperprolactinaemia and sexual impotence in men. Indeed, a low libido level is currently considered the most critical behavioral change in hyperprolactinaemic subjects. However, prolactin has a broader action on reproduction that appears at first sight. In fact, this hormone normally serves as a stimulator of genital function in animals (for a review, see: Bartke, 1976). Chronic moderate hyperprolactinaemia induced by pituitary homografts is accompanied by an increase in the weight of the seminal vesicles and the ventral prostate in male rats (Doherty et al., 1980). However, high levels of prolactin may cause hypogonadism and inhibition of spermatogenesis in men (Thorner et al., 1974; Franks et al., 1978).

Hyperprolactinaemia, as induced by pituitary microadenomas, is associated with sexual impotence in men (Besser and Thorner, 1975; Buvat et al., 1978; Horrobin, 1974; Legros et al., 1978) and women (Thorner, 1977; McNeilly, 1980). However, whether these patients experience a loss of sexual drive is debated (Franks et al., 1978; Perryman and Thorner, 1981). The same has been shown in animals with chronic hyperprolactinaemia induced by pituitary homografts (Svare et al., 1979) or after peripheral injection of large doses of the hormone (Hartmann et al., 1966).

In contrast, increased levels of plasma prolactin are detected in male rats exposed to a receptive female before mating (Kamel et al., 1977) and in men during sexual intercourse (Robyn, 1971). The same has been found after sexual activity in male and female animals (Convey et al., 1971; Kamel et al., 1975; Neill, 1980). The effects of prolactin on male sexual behavior have been described as null, facilitatory or inhibitory according to the treatment (Drago, 1984; Mas, 1995).

The apparent discrepancies among these data prompted us to study the sexual performance of male rats, using the short-term hyperprolactinaemia model. In 1981, we found that shortly after the beginning of moderate hyperprolactinaemia, latency to the first mount and to intromission was reduced and the frequency of mounts and intromissions was increased (Drago et al., 1981b). This paradoxical stimulation of male sexual activity by short-term, moderate hyperprolactinaemia is similar to that described in animals with hyperprolactinaemia induced by systemic administration of domperidone, which increases the frequency of mounts and intromissions (Bailey and Herbert, 1982; Nasello et al., 1997). Further, central prolactin injections have been reported to be neurochemically and behaviorally effective in inducing maternal behavior (Bridges et al., 1990) and ineffective in inducing sexual behavior (Laping and Ramirez, 1990).

In order to compare the effects of short-term endogenous hyperprolactinaemia and injected prolactin on male sexual activity, we administered s.c. rat prolactin dissolved in saline to male rats with poor sexual activity. Male rats of the Wistar strain (Charles River, weighing 200–250 g) were used. Three categories of animals were selected: rats with normal sexual performance showing at least one ejaculation in a 30-min test; rats showing only mounts and intromissions without any ejaculation latency equal to 1800 s), which were considered as sexually sluggish rats; and rats that showed no mounts, intromissions or ejaculations at all (impotent rats). The sexual activity of these rats was evaluated after four mating tests with receptive females, at weekly intervals. Copulatory behavior was assessed according to Beach (1956). The following behavioral parameters were scored for each animal, using an event recorder (Basile, Italy). Latency (in s) to the first mount and intromission was the time from the introduction of the female into the male's cage until the first mount or intromission, respectively. Latency (in s) of ejaculation was the time from the first intromission until the first ejaculation. Frequency of mounts and intromissions was the total number of mounts or intromissions in a series. Frequency of ejaculations was the total number of ejaculations during a 30-min observation period. The behavioral test was terminated after 30 min (1800 s). A latency of

Table 1
Frequency of mounts, intromissions, and ejaculations of sexually inactive (impotent) rats and of sexually sluggish animals after acute injection of rat prolactin

	Mounts (total number)	Intromissions (total number)	Ejaculations (total number)
Normal			
Saline	37.0 ± 3.9	39.6 ± 4.0	1.0 ± 0.2
Prolactin (5 μg/kg)	51.1 ± 4.0[a]	53.1 ± 4.7[a]	2.1 ± 0.2[a]
Prolactin (10 μg/kg)	53.1 ± 5.0[a]	53.6 ± 5.0[a]	2.0 ± 0.2[a]
Prolactin (50 μg/kg)	59.7 ± 4.8[a]	61.0 ± 4.8[a]	2.1 ± 0.3[a]
Sluggish			
Saline	28.1 ± 2.1	29.3 ± 2.5	0.0 ± 0.0
Prolactin (5 μg/kg)	39.6 ± 3.2[a]	41.1 ± 4.1[a]	1.5 ± 0.1[a]
Prolactin (10 μg/kg)	48.6 ± 4.3[a]	53.9 ± 5.4[a]	1.8 ± 0.1[a]
Prolactin (50 μg/kg)	28.1 ± 2.2	31.0 ± 3.0	0.2 ± 0.0
Impotent			
Saline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Prolactin (5 μg/kg)	42.4 ± 4.8[a]	51.3 ± 5.7[a]	1.4 ± 0.5
Prolactin (10 μg/kg)	53.2 ± 5.0[a]	63.1 ± 5.1[a]	1.5 ± 0.2
Prolactin (50 μg/kg)	0.6 ± 0.0[a]	0.6 ± 0.0[a]	0.0 ± 0.0

Values are means ± S.E.M. of total number of events over a 30-min period. Each experimental group consisted of seven animals. The ANOVA revealed a significant drug effect with $F(2,27) = 34.6$ ($P < 0.05$ for impotent rats) and 28.1 ($P < 0.05$ for sluggish rats).

[a] Significantly different as compared to saline-injected controls ($P < 0.05$, post-hoc Dunnett's test for multiple comparisons).

1800 s was attributed to those animals not showing any specific behavioral item. Mating tests were carried out during the late scotophase (10 h after the onset of darkness), under dim red light.

Ovariectomized females, as copulatory partners, were used for experimental sessions a week after bilateral operation. They were made sexually receptive by s.c. injection of estradiol benzoate (60 μg/kg in olive oil) followed 48 h later by s.c. injection of progesterone (1 mg/kg in olive oil). Both drugs were supplied by Sigma (USA).

Interestingly, we found that the s.c. injection of prolactin (5, 10 or 50 μg/kg) did not modify the latency (data not shown) but increased the frequency of mounts, intromissions and ejaculations of normal rats (Table 1). Furthermore, acute s.c. injection of prolactin 5 or 10 μg/kg (but not 50 μg/kg) stimulated sexual behavior in both impotent and sluggish rats and induced a full pattern of copulatory behavior in these animals. In fact, prolactin induced the appearance of mounts, intromissions and ejaculations in impotent rats (Table 1). In sluggish rats, acute injection of prolactin (except for the dose of 50 μg/kg) reduced the mean latency to the first mount or intromission (data not shown) and increased the frequency of mounts and intromissions (Table 1). Furthermore, it induced sluggish rats to ejaculate during the mating test.

4. The paradoxical stimulation of female behavior by prolactin

Contrasting data also exist regarding the effects of prolactin on female sexual behavior. Dudley et al. (1982) reported an inhibition of lordosis behavior in female rats after i.c.v. injection of prolactin or with chronic hyperprolactinaemia. A loss of sexual activity has been described in lactating female rats (Sodersten et al., 1983) and in hyperprolactinaemic women (Heiman et al., 1991; Karpas, 1992; Sobrinho, 1993). In contrast, Harlan et al. (1983) reported stimulation of lordosis in female rats after infusion of prolactin in the midbrain. Stuart et al. (1987) and Alder et al. (1986) found no correlation between plasma prolactin levels and loss of sexual activity in women.

We recently studied the effects of low doses of rat prolactin on lordosis behavior in female rats. The animals were ovariectomized as described above, treated with estradiol benzoate and progesterone at the doses indicated and exposed to an active male rat for a 30-min mating test. The lordosis quotient (number of lordoses shown by female/number of mounts shown by male) was measured using an event recorder (Basile, Italy) according to the method described by Pfaff (1973). One hour prior to behavioral testing, some of the females received a prolactin s.c. injection (5, 10 or 50 μg/kg). Results showed that the lordosis quotient of ovariectomized rats was higher after s.c. injection of prolactin 5 or 10 μg/kg. Again, the dose of 50 μg/kg was inactive in this respect (Fig. 2).

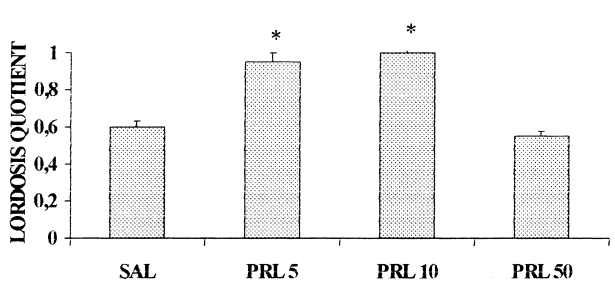

Fig. 2. Effects of rat prolactin on lordosis behavior (expressed as lordosis quotient) of ovariectomized female rats treated with estradiol benzoate and progesterone. Values are mean ± S.E.M. Each experimental group consisted of seven animals. Prolactin (5, 10 or 50 μg/kg) was injected s.c. 1 h prior to 30-min behavioral testing. For the procedure of behavioral test, see text. * Significantly different as compared to saline-injected animals ($P < 0.05$, Dunnett's test for multiple comparisons).

5. Discussion

The present results indicate that low doses of prolactin stimulate novelty-induced grooming in rats. A paradoxical effect of low doses of prolactin on male and female sexual behavior was also observed, suggesting that, like short-term hyperprolactinaemia, acute low doses of this hormone may facilitate rather than inhibit this behavior. Numerous findings suggest that sexual performance is accompanied (Robyn, 1971; Kamel et al., 1977) or preceded (Convey et al., 1971; Kamel et al., 1975; Neill, 1980) by increased plasma prolactin levels in male subjects of various experimental species and in men. In addition, during the estrous cycle of female rats, a surge of prolactin has been described prior to the onset of sexual behavior, suggesting an interaction between this hormone and sexual receptivity (Neill, 1980). The hyperprolactinaemia found during sexual activity seems to be independent of the experimental manipulation of animals (Kamel et al., 1977).

Since prolactin enters the brain by active transport mechanisms (Walsh et al., 1987; Felicio and Bridges, 1992), it may be that these mechanisms are readily saturated and that higher plasma levels of the hormone do not further increase its behavioral effects.

Various central effects have been attributed to prolactin. The hormone stimulates the turnover of dopamine in the nucleus accumbens (Fuxe et al., 1977) and can counteract the testosterone-induced inhibition of dopamine turnover in the preoptic area (Kalra et al., 1981). Since brain dopamine has been found to be involved in the stimulation of novelty-induced grooming (Cools et al., 1978) and male sexual behavior in rats (Tagliamonte et al., 1974; Paglietti et al., 1978), the facilitatory effect of low doses of prolactin on novelty-induced grooming and male sexual behavior may be due to stimulation of central dopamine

neurotransmission. Furthermore, prolonged stimulation of brain dopamine neurotransmission by chronic hyperprolactinaemia may cause hyposensitivity of this neural mechanism (Drago, 1984). Thus, the duration of hyperprolactinaemia is also important for the expression of the behavioral effects of prolactin.

The facilitatory effect of acute s.c. injection of rat prolactin on male sexual behavior is similar to the effect of 5-day hyperprolactinaemia induced by intraperitoneal injections of domperidone (Nasello et al., 1997). In contrast, sexual activity of male rats was reduced after 60-day domperidone-induced hyperprolactinaemia (Cruz-Casallas et al., 1998). Recently, it was found that sexual motivation, induced by an encounter with a sexually proceptive female, promotes oxytocin and prolactin secretion in sexually naive male rats (Hillegaart et al., 1998). An interesting hypothesis is that the effects of prolactin on erectile function are independent of effects on sexual behavior and that the inhibitory effects of chronic hyperprolactinaemia on sexual arousal are linked to the effects of hyperprolactinaemia on luteinizing hormone (LH) release (Doherty et al., 1990). The present results are consistent with those of Cruz-Casallas et al. (1999) showing that a single i.c.v. injection of ovine prolactin (10 μg) to male rats facilitates sexual activity and increases extracellular striatal levels of various dopamine metabolites. In contrast, five daily i.c.v. injections of the hormone decreased sexual behavior and reduced striatal concentrations of dopamine metabolites. Although this i.c.v. dose of prolactin seems rather high, it should be noted that in this case a heterologous prolactin was used. Thus, acute and chronic central prolactin treatments have both stimulatory and inhibitory effects on the sexual behavior of male rats and the opposite effects on dopamine neurotransmission may explain this dual action of the hormone.

It is more difficult to explain prolactin effects on female sexual behavior, as dopamine neurotransmission does not play a crucial role in this behavior (Pfauss and Everitt, 1995). Interestingly, dopamine and serotonin seem to interact in the modulation of prolactin release and sexual behavior of lactating female rats (Jahn et al., 1999). Thus, the effects of acute injection of low doses of prolactin or short-term hyperprolactinaemia on female sexual behavior could possibly be explained by actions of this hormone on neurotransmitters other than dopamine.

6. Concluding remarks

The "low-dose" concept is now known to apply also to behavioral effects of prolactin. This concept was repeatedly expressed in the whole titanic work of De Wied. He clearly showed that the effects of neurohypophyseal nonapeptides, vasopressin and oxytocin on memory processes have physiological significance (De Wied, 1979). For instance, a single injection of 0.6 or 1.8 μg lysine–vasopressin has a long-term dose-dependent effect on extinction of the pole jumping avoidance response. The effect persists for days beyond the actual presence of the peptide in the organism (De Wied, 1971). This not only suggests that the physiological effects of neuropeptides on the brain may be elicited by low plasma concentrations of these neuropeptides, but also that these effects are long-lasting. This, I believe, is among the most important De Wied's discoveries.

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