REPRODUCTION
REVIEW

Prolactin secretion patterns: basic mechanisms and clinical implications for reproduction

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Abstract

Prolactin (PRL) is one of the most versatile hormones in the mammalian body affecting reproductive, sexual, metabolic, immune, and other functions. It is therefore not surprising that the neural control of PRL secretion is complex, involving the coordinated actions of several hypothalamic nuclei. A plethora of experimental data exists on the hypothalamic control of hormone secretion under various physiological stimuli. There have been even mathematical models and computer studies published, which help to understand the complex hypothalamic–pituitary network. Nevertheless, the putative role of PRL for human reproduction still has to be clarified. Here, we review data on the underlying mechanisms controlling PRL secretion using both experimental and mathematical approaches. These investigations primarily focus on rhythmic secretion in rats during early pregnancy or pseudopregnancy, and they point to the important role of oxytocin as a crucial PRL-releasing factor. Recent data on human studies and their theoretical and clinical implications are reviewed as well. In particular, studies demonstrating a sustained PRL surge after sexual climax in males and females are presented, indicating possible implications for both sexual satiation and reproductive functions. Taking these data together, there is evidence for the hypothesis that the PRL surge induced by sexual activity, together with the altered PRL rhythmic pattern, is important for successful initialization of pregnancy not only in rodents but also possibly in humans. However, further investigations are needed to clarify such a role in humans.
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Introduction

Prolactin (PRL) is an exceptional hormone with important implications for reproduction and sexual behavior (Ben-Jonathan *et al*. 2008). More than 300 biological functions, for example immune functions, osmoregulation, reproduction, and behavior, have been described so far, and its pleiotropic features are unique (Freeman *et al*. 2000, Grattan & Kokay 2008).

PRL secretion from lactotrophs of the anterior lobe of the pituitary gland is controlled by stimulatory as well as inhibitory factors. Ambient lighting conditions entrain PRL surges to the particular time (Bethea & Neill 1979, 1980) of day possibly via actions of the suprachiasmatic nucleus (SCN) that is regarded as the master clock in mammals (Reppert & Weaver 2002). We investigated the underlying mechanisms that control PRL secretion by using a joint biological/mathematical approach. Mathematical modeling and computer studies represent an innovative approach to understand the complex hypothalamo-pituitary network (Leng & Macgregor 2008). In addition, we aimed to elucidate the role of PRL in human sexual behavior and reproduction. Until recently, human studies were rare, mainly focusing on states of chronic hyperprolactinemia and the implications for sexual and reproductive function. Therefore, we have systematically investigated the role of serum PRL in human male and female sexual behavior and have developed theoretical models on the potential physiological significance of PRL in humans.

Accordingly, this review aims to highlight some important physiological features of PRL secretion patterns. Moreover, we summarize essential findings on altered PRL secretion patterns in animals and humans, discuss the implications for reproductive functions, and disclose promising future investigations.

Secretory rhythms of pituitary hormones

Hormone secretion in mammals is precisely balanced to the needs of the organism in its current state. The final concentration of several circulating pituitary

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hormones is defined by releasing and/or inhibiting factors originating from hypothalamic nuclei mainly. These nuclei in turn are controlled by hierarchically higher brain sites, which have an integrative function. The afferent inputs to these integrative sites may be of neural or hormonal origin. Furthermore, neural networks controlling hormone secretion often include feedback loops in which the secreted signaling molecule modifies its own secretion pattern either directly or indirectly.

Some endocrine systems exhibit secretion patterns with a period of 24 h. These circadian rhythms oscillate usually in relation to the ambient light/dark cycle and are in synchronization with physiological rhythms like the sleep/wake cycle or the daily fluctuation of the body temperature. Studies have shown that mammalian organisms possess a central pacemaker in the brain which functions like a body clock (Schibler & Sassone-Corsi 2002). This pacemaker is represented in the SCN and governs peripheral oscillators, which are responsible for physiological output rhythms (Reppert & Weaver 2002). Further features of the central pacemaker are the generation of an endogenous activity rhythm under temporal isolation and the entrainment of this rhythm to external time cues like the ambient light/dark cycle (Reppert & Weaver 2002).

It is reasonable to assume that the central rhythm generator is involved in the generation of circadian secretory rhythms. Indeed, lesion studies demonstrated that after ablation of the central pacemaker, most of the secretory rhythms vanish (Refinetti *et al*. 1994, Warren *et al*. 1994, Weaver 1998). Thus, besides the highly complicated mechanism through the action of releasing/inhibiting factors that control the amount of hormones which is secreted, there appears to be an additional system assuring appropriate timing of hormone surges.

One aspect of our research has been dedicated to the mechanisms responsible for entrainment, generation, and expression of secretory rhythms of the pituitary hormone PRL. The secretory profile of PRL is well established in female rats, showing three distinct secretory patterns that are related to particular physiological stages (Fig. 1). As extensively demonstrated by scientific experiments, the level of circulating PRL remains low in normal cycling rats throughout most of the estrous cycle. There is just one prominent PRL surge at proestrus, which is coincidental with LH during the cycle that has a period of 4–5 days (Fig. 1A; Freeman *et al*. 2000). A second type of PRL secretory pattern involves pups suckling on the mother animal. In this situation, PRL secretion is induced via a neuroendocrine reflex arc (Fig. 1B). As soon as pups start to suckle, PRL secretion increases and, depending on how many pups are suckling, higher values of circulating PRL can be measured. A third pattern can be observed for 10 days during pregnancy and 12 days during pseudopregnancy in response to the mating stimulus. This rhythmic pattern consists of an increase in PRL secretion in the early morning (0100–0300 h, nocturnal surge) and late afternoon (1400–1800 h, diurnal surge) (Freeman & Neill 1972, Freeman *et al*. 1974, Smith *et al*. 1975; Fig. 1C).

During the past few years, we have been investigating potential mechanisms involved in controlling PRL secretion in rats. This includes the design of mathematical models based on experimental data

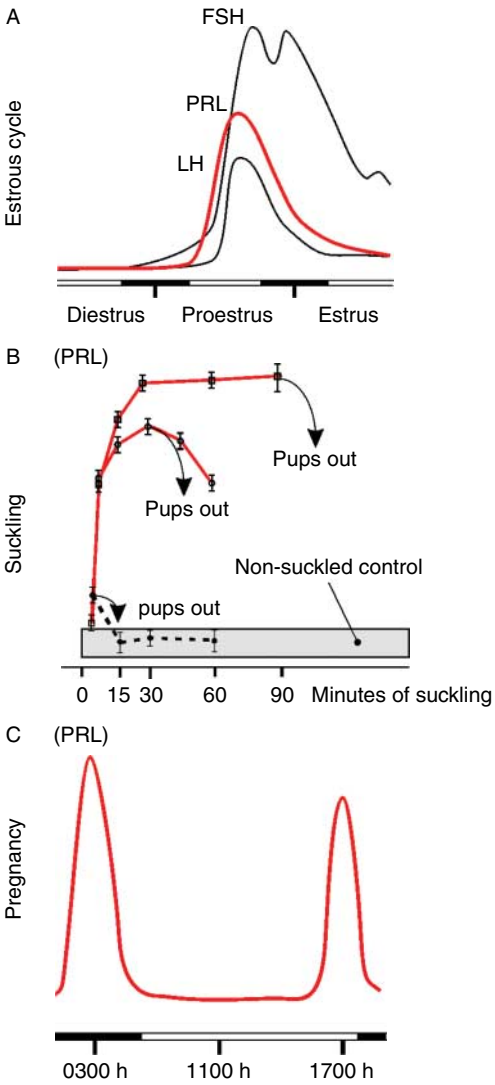

Figure 1 Different PRL secretory patterns of female rats. (A) Schematic representation of the LH, FSH, and PRL levels during the estrous cycle in normal animals (Erskine 1995). (B) Schematic representation of the PRL response of a nursing rat to the suckling stimulus of one, four, and six pups respectively. The PRL magnitude correlates with the number of suckling pups and the duration of suckling. Adapted, with permission, from **Grosvenor CE, Shyr SW, Goodman GT & Mena F** 1986 Comparison of plasma profiles of oxytocin and prolactin following suckling in the rat. *Neuroendocrinology* **43** 679–685. © 1986 S. Karger AG, Basel. (C) Schematic representation of the mating-induced PRL secretion pattern. The surges occur autonomously every day at around 0300 and 1700 h for 10–14 days (Egli *et al*. 2004). For a comparable figure on multiple modes of prolactin secretion, see also Grattan & Kokay (2008).

collected in parallel. The results gathered led to the identification of a neural network that allows the simulation of several secretory rhythms of PRL known in rats (Egli *et al.* 2004, 2006, Bertram *et al.* 2006). Computer simulations illustrate the interplay between releasing and inhibiting factors to generate PRL secretory patterns in normal cycling as well as pregnant/pseudopregnant rats.

Proposed neural network in charge of PRL secretion

Secretion from lactotrophs is controlled by stimulatory and inhibitory inputs supplied by neurosecretory cells in the hypothalamus via the portal vessel system (Arey *et al.* 1989, Lamberts & Macleod 1990, Freeman *et al.* 2000). The PRL-inhibiting factor is dopamine (DA), and this plays the most prominent role in PRL secretion (Lamberts & Macleod 1990, Ben-Jonathan & Hnasko 2001). It is released by three hypothalamic neural populations: i) periventricular hypothalamic dopaminergic neurons, ii) tuberohypophyseal neurons, and iii) tuberoinfundibular neurons of the arcuate nucleus (Freeman *et al.* 2000). One PRL-releasing factor candidate is oxytocin. One daily stimulatory rhythm regulating PRL secretion is unveiled in ovariectomized (OVX) rats in which the DA receptor is blocked at varying times throughout the day (Arey *et al.* 1989). It was possible to block this rhythm with an oxytocin antagonist, suggesting that oxytocin stimulates PRL secretion (Arey & Freeman 1989, 1992). Furthermore, a prominent oxytocin surge during the afternoon can be measured in the serum of cervically stimulated rats (inducing pseudopregnancy). This surge is coincident with the diurnal PRL surge (Egli *et al.* 2004, Bertram *et al.* 2006). All these experimental results together indicate that oxytocin is a physiological releasing factor of PRL.

Both DA and oxytocin neurons seem to be influenced by neurons in the SCN. Vasoactive intestinal peptide (VIP) fibers originating in the SCN innervate DA neurons in the arcuate nucleus (Gerhold *et al.* 2001), and more recent data suggest that VIP fibers also innervate oxytocin neurons in the periventricular nucleus (PVN; Egli *et al.* 2004).

Mathematical modeling of PRL secretion patterns in rats

In order to analyze the core principles of the PRL secretion controlling system and to illustrate the dynamic interactions, mathematical modeling was applied. Because modeling requires a reduction of the actual system to core functions, the most important network parameters were selected (Fig. 2). Thereafter, equations were designed which describe the behavior of the selected parameters in the neural network.

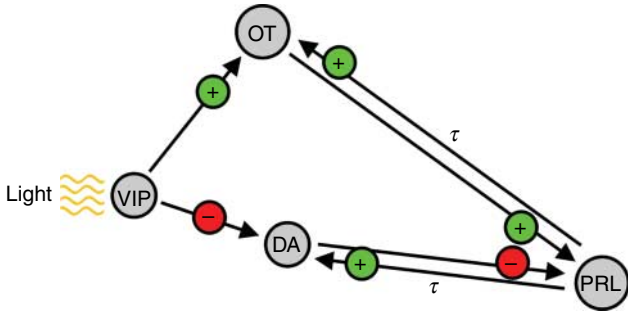

Figure 2 Sketch of the proposed neural network used for mathematical modeling of PRL secretion patterns. DA, population of dopaminergic neurons of arcuate nucleus; OT, population of oxytocinergic neurons of the periventricular nucleus; PRL, lactotrophs of the anterior lobe of the pituitary gland; VIP, population of SCN neurons transmitting timing signals via vasoactive intestinal peptide. The symbols + and − indicate the characteristics of the input (stimulatory or inhibitory). τ denotes the time delay.

All equations together form a phenomenological model of PRL secretion.

The modeling process was started by describing the interaction between the hypothalamic DA neurons and pituitary lactotrophs only. As previously mentioned, DA predominantly inhibits PRL secretion. PRL in turn feeds back time delayed on the DA neurons stimulating DA synthesis and secretion (Gudelsky & Porter 1980, DeMaria *et al.* 1999, Lerant *et al.* 2001). Thus, PRL causes activation of DA neurons, which suppress their own PRL secretion (Bertram *et al.* 2006). This kind of feedback loop produces autonomous oscillation of the partners after initial perturbance. This means that the underlying mechanism responsible for PRL oscillation in early pregnant or pseudopregnant rats could be based on the described feedback loop between hypothalamic DA neurons and pituitary lactotrophs (Bertram *et al.* 2006).

Additional parameters, such as oxytocin, which is an important player in PRL secretion (Egli *et al.* 2004), have been included in the mathematical model in the second step. Up to now, only controversial data are available regarding the PRL effect on oxytocin containing periventricular neurons (Ghosh & Sladek 1995, Kokay *et al.* 2006, White & Samson 2006). The mathematical model is based on the assumption that PRL exerts a stimulatory influence on oxytocin containing PVN cells. However, additional experiments need to be carried out in the future to elucidate the real nature of the PRL influence on oxytocin containing PVN neurons.

Since PRL secretion entrains to the ambient light/dark cycle (Bertram *et al.* 2006), further parameters were introduced into the mathematical model to allow interaction between the lighting conditions and the timing of the PRL surges.

Figure 3A, C, and E show the simulation of the PRL rhythm of early pregnant/pseudopregnant rats calculated by the mathematical model that comprises three

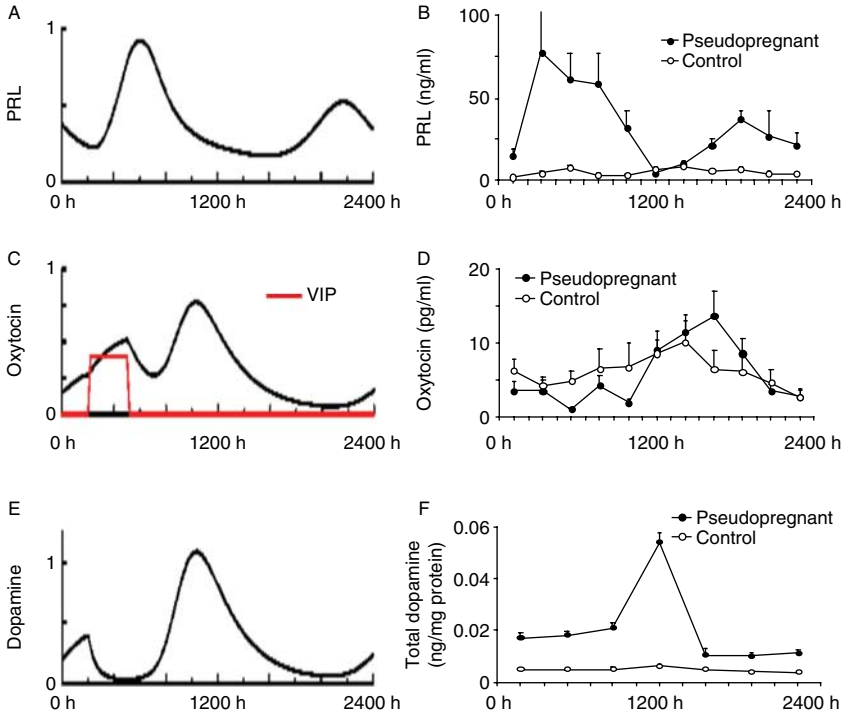

Figure 3 Comparison of the simulation and the experimental data measured in rats. The simulation of PRL secretion (A) is remarkably similar to the measured fluctuation in pseudopregnant animals after cervical stimulation (B, filled circles). In contrast, PRL values of untreated animals (not stimulated) do not show fluctuation (B, open circles). Similarly, the calculated (C) and the determined oxytocin release patterns (D) are comparable. However, the calculated oxytocin surge appears shortly before the values peak in rats. The VIP timing signal is included in C (red). Calculated dopamine values (E) match the actual fluctuation measured in pseudopregnant rats (F).

equations (for a detailed description of the model, see Egli *et al.* (2004)). The actual experimental values measured in the animals are displayed in the second column of Fig. 3B, D, and F. In the model, oxytocin (PRL-releasing factor), which is released in response to the mating stimulus (Egli *et al.* 2006), serves as a trigger signal to induce a PRL surge. This first PRL surge perturbs the hypothalamo-pituitary PRL–DA system and switches on the oscillatory PRL secretion as described earlier (Fig. 3A). In addition, VIP in the morning exerts a depressing effect on DA activity. Thus, the elevated VIP value (Fig. 3C, red) reduces DA activity (Fig. 3E). The reduction in DA lowers the inhibitory tone to the lactotrophs, enabling the occurrence of a prominent nocturnal (early morning) PRL surge (Fig. 3A). Therefore, VIP facilitates the occurrence of the nocturnal PRL surge, and at the same time, it is entraining the PRL rhythm to a 24 h period. Without the periodic VIP release, the morning PRL surge would drift due to the free-running DA–PRL rhythm (with periods >24 h, data not shown). In addition, the VIP influence causes PRL surges of different magnitude (Fig. 3A). This asymmetry of the PRL surges is typically observed in early pregnant/pseudopregnant rats (Fig. 3B; Smith *et al.* 1975). The diurnal (late afternoon) PRL surge in this mathematical model is solely driven by oxytocin (Fig. 3C and D). DA oscillation is perfectly out of phase with PRL (Fig. 3A, B, E, and F).

Although the mathematical model presented consists of three equations only, it is capable of reproducing the main characteristics of the PRL secretory rhythm of early pregnant/pseudopregnant rats (Fig. 3B, D and F). Furthermore, it suggests possible temporal releasing patterns for the PRL stimulatory and inhibitory factors oxytocin and DA, as well as for the timing signal VIP, which are necessary for generating the PRL rhythms (Fig. 3A). To illustrate the additional phases of pregnancy, more sophisticated mathematical models are necessary, similar to the ones we published earlier (Bertram *et al.* 2006). These models have been developed further and also take into account the termination of the oscillatory PRL secretion pattern that is based on a sustained increase in DA release associated with the onset of placental lactogen secretion (Grattan & Kokay 2008). The models, however, do not simulate the hyperprolactinemia situation of late pregnancy and lactation, which are most likely due to diminished responsiveness of the tuberoinfundibular DA (TIDA) neurons to PRL feedback (Arbogast & Voogt 1996). This in turn – at least for lactation – seems to be caused by suckling stimulus-induced suppression of tyrosine hydroxylase, the rate-limiting enzyme in DA biosynthesis, and gene expression in the TIDA neurons of pup-exposed dams. Moreover, there are some differences between rat and human physiology in the sense that chronically elevated PRL occurs in human pregnancy from at least week 10 (Boyar *et al.* 1975), in contrast to the pulsatile secretion in rats. Possibly, adaptive changes in the network controlling PRL secretion in humans occur earlier than in rats. However, this needs further investigation.

Thus, the mathematical models presented were designed for the PRL secretion in rats and cannot be applied to humans without modifications. As critical

parameters of the PRL secretion controlling system in humans are missing, this impedes the design of a detailed mathematical model. Nevertheless, the rat still serves as an indispensable source of information on the neuroendocrine regulation of PRL secretion (Ben-Jonathan *et al*. 2008), and thus the rat model is a very valid guide for a future human model.

PRL secretion patterns in humans and the clinical implications

PRL is involved in the regulation of several human reproductive functions mainly via the modulating effects of gonadotropins (Kelly *et al*. 1993). Furthermore, PRL seems to play a critical role in human ovarian function due to the observation that hyperprolactinemia facilitates the development of amenorrhea and modifications of the luteal phase of the menstrual cycle (Kauppila *et al*. 1988). Levels of circulating PRL between 3 and 15 μg/l are considered necessary for maintaining normal reproductive function, and levels below and above are associated with an increased rate of infertility (Kauppila *et al*. 1988). Even though hypoprolactinemia does not cause major clinical problems, a minimum concentration between 1 and 3 μg/l is thought to be necessary for the physiological regulation of ovarian function (Schwarzler *et al*. 1997).

Menstrual cycle

PRL patterns in women are similar to those elucidated in female rats. There is some evidence that a PRL surge occurs during ovulation coincident with the secretory peak of LH as in rodents (Vekemans *et al*. 1977, Suganuma *et al*. 1988), although the extent seems to be much weaker in women than in rats (Ben-Jonathan *et al*. 2008). Furthermore, in comparison to the normally low circulating levels of PRL (5–25 ng/ml; Kacsoh 2000), elevated levels have been reported in the late follicular phase and during the luteal phase of the normal menstrual cycle (L'Hermite & Robyn 1972, Brumstead & Riddick 1992), which might – at least partly – be due to an increase in estradiol. However, currently available data on the effect of estradiol in the regulation of PRL secretion in humans are controversial (Ben-Jonathan *et al*. 2008). In contrast to rodents, the normal daily PRL secretory profile of humans displays a distinct circadian pattern characterized by a rise during nocturnal sleep and a rapid fall after awakening (Kawagoe *et al*. 1988). This 24 h pattern shows the same features throughout the menstrual cycle, but the levels are generally higher during the luteal phase than during the follicular phase (Kawagoe *et al*. 1988). It is still controversial whether this daily PRL secretory pattern follows the sleep–wakening cycle or the circadian rhythm.

Corpus luteum

Successful pregnancy involves a series of physiological changes in the conceptus, uterus, and ovaries/corpus luteum in women. Major goal of these changes in early pregnancy is to prevent the functional and structural degradation of the corpus luteum (luteolysis), which would terminate progesterone secretion. Studies have shown that PRL-receptor (PRLR) in preovulatory granulosa cells may be involved in the coordination between granulosa cells and follicular macrophages in the process of ovulation (Vlahos *et al*. 2001). In humans, the lifespan of the corpus luteum after ovulation is sufficient to allow movement of the early embryo through the oviduct, preparation of the uterus for implantation, and the embryo invasion of the endometrium (Csapo & Pulkkinen 1978). However, the regression of the corpus luteum in the course of the normal cycle takes place just before the developing placenta produces sufficient progesterone to keep the uterus in a supportive state until the end of gestation (Stouffer & Hearn 1998). Therefore, it is crucial for the continuation of pregnancy after egg fertilization that maternal recognition occurs to signal the extension of luteal function, at least until the essential activities are replaced by placental functions (luteal–placental shift). During this period, human chorionic gonadotropin (hCG) is one of the major and well-established factors in the recognition of pregnancy. HCG is produced and secreted by the syncytiotrophoblast into the maternal compartment where it plays a key endocrine role (Katabuchi & Ohba 2008). It also stimulates syncytiotrophoblast formation in an autocrine manner (Handschuh *et al*. 2007). Its secretion by the trophoblast together with LH secretion is essential for the secretory maintenance of the corpus luteum. Nevertheless, it is surprising that despite the importance of maternal recognition in the first phase of human pregnancy, very little data exist on the underlying pathophysiology (Stouffer & Hearn 1998). Although PRL is a luteotrophic hormone in rodents, its role in the regulation of the corpus luteum differs greatly in mammalian species (Niswender *et al*. 2000). In humans, hypo- as well as hyperprolactinemia may cause luteal function deficiency (Garcea *et al*. 1983, Hunter 1984, Kauppila *et al*. 1988, Gu 1993).

Significantly elevated concentrations of PRL are detected in cytosolic extracts of premenopausal ovaries than in postmenopausal ovaries (Schwarzler *et al*. 1997). Evidence of a direct effect of PRL in steroidogenesis is given by several studies showing the expression of PRLR on human-luteinized granulosa cells (Alila *et al*. 1987, Schwarzler *et al*. 1997, Vlahos *et al*. 2001). McNatty *et al*. (1974) have even discovered that the effect of PRL on steroidogenesis is dose-dependent, showing doses <100 ng/ml as stimulating and doses above 100 ng/ml as inhibiting progesterone production.

Therefore, PRL might also be expected to assist in the maintenance of progesterone production (Perks *et al*. 2003). Interestingly, *in vitro* studies showed that a high level of PRL increased progesterone only in midcycle cells during the initial 48 h of culture (Alila *et al*. 1987). The fact that PRL can be localized by immunostaining in the human corpus luteum but not in the ovarian stroma further supports its role in luteal function (Khan-Dawood 1988). *PRLR* transcripts were detected in the extracted RNA of mature follicles, but no detectable staining was noted in secondary and early antral follicles, which suggests that the effects of PRL are exerted around the time of ovulation (Vlahos *et al*. 2001).

Pharmacological suppression of PRL secretion by a high dose of bromocriptine (DA receptor agonist) causes a moderate reduction in plasma progesterone (Schulz *et al*. 1978, Richardson *et al*. 1985). McNatty *et al*. (1974) demonstrated that a high concentration of PRL in the follicular fluid may depress the progesterone secretion by granulosa cells. Higher concentrations of PRL may reduce 17β-estradiol production induced by hCG in human luteal cells *in vitro* (Tan & Biggs 1983). On the other hand, the production of progesterone and estrogen was higher when hCG was applied in combination with PRL than when hCG only was applied (Hunter 1984). PRL inhibits the catabolism of the corpus luteum and is responsible for maintaining a large number of LH and estradiol receptors (Leroy-Martin *et al*. 1989). PRL may also contribute significantly to early corpus luteum formation and survival by acting as a potent antiapoptotic factor for human granulosa cells (Perks *et al*. 2003). Such a correlation is supported by the observation that there were lower levels of apoptosis in the granulosa cells of women undergoing IVF who conceived (Perks *et al*. 2003). It is therefore likely that the increased PRL level during pregnancy exerts a regulatory function on the steroidogenesis of human luteal tissue (Hiroi 1988, Gu 1993), which is, in turn, crucial for successful pregnancy.

So far both hyper- and hypoprolactinemia have been investigated in the context of follicular and corpus luteum function, but there is no information available as to whether release patterns of PRL are associated with pathological situations. Differences in the PRL secretion rhythm might disturb conception and early pregnancy, as described for LH in combination with PRL (Soules *et al*. 1989). For example, women with luteal phase deficiency show different PRL pulse amplitudes in the early follicular phase in comparison to normal women (Soules *et al*. 1991). These abnormalities are associated with definite alterations in gonadotropin secretion (Soules *et al*. 1991). The specific binding of LH in human luteal tissue is reduced in the presence of very high or very low levels of PRL (Garcea *et al*. 1983). Results from Hinney *et al*. (1995) support the finding that PRL episodes in combination with LH pulses regulate progesterone and estradiol secretion in the human corpus luteum, i.e. PRL pulses are necessary for the effect of LH pulses. These results show different secretion patterns during the menstrual cycle, with the highest incidence of coincident LH and PRL pulses during the mid- and late luteal phases. Studies have shown that some women show a close correlation between increased estradiol secretion, as well as progesterone secretion, and the prior occurrence of LH and PRL pulses (Hinney *et al*. 1995). In contrast, other women show fluctuation of both gonadal steroids with no particular correlation to LH surge. This suggests a certain degree of autonomy in the regulation of the corpora lutea (Hinney *et al*. 1995). Although the clinical implications of these differences have not yet been investigated, it seems likely that they might also be associated with differences in reproductive function.

Sexual behavior and reproduction

To better understand the physiological role of PRL in reproduction and sexual behavior in humans, we have systematically investigated PRL plasma during the sexual response cycle in females and males. A series of studies showed that orgasm in humans induces pronounced and long-lasting secretion of peripheral PRL with significantly higher levels of PRL in females (Fig. 4; Exton *et al*. 2001). This effect was not observed during sexual arousal *per se* (Kruger *et al*. 1998, 2003*a*, Exton *et al*. 1999, 2000). Furthermore, the magnitude of the PRL increase following intercourse was 400% greater than following masturbation, which may indicate the biological significance of cervicovaginal stimulation and/or physical contact with a partner (Brody & Kruger 2006). The results lead us to formulate two theories on the function of increased PRL levels after sexual activity (Fig. 5). First, PRL may take part in a sexual satiation mechanism indicating a reduced dopaminergic tone in hypothalamic brain areas after orgasm and/or serving as a negative feedback on dopaminergic neurons in mesolimbocortical, nigrostriatal, and other diencephalic brain areas that are crucial for appetitive behavior and reward (Kruger *et al*. 2002). Second, in parallel to animal studies, PRL might be a part of an orgasm-induced neuroendocrine reproductive reflex optimizing fertility and conception. Regarding the first hypothesis, we have systematically altered PRL plasma levels in order to investigate the effects on acute sexual drive and function. Since PRL and its antagonists are not available for use in humans, PRL levels were pharmacologically altered using TRH for increasing PRL levels, and DA receptor agonist (cabergoline) for decreasing them (Kruger *et al*. 2003*b*). Although this methodological approach has some limitations, this study provided evidence of close interaction between increased, decreased, or restored PRL levels and sexual drive and function, with the highest values on the acute sexual experience scale (ASES) in the low PRL condition and lowest values on the

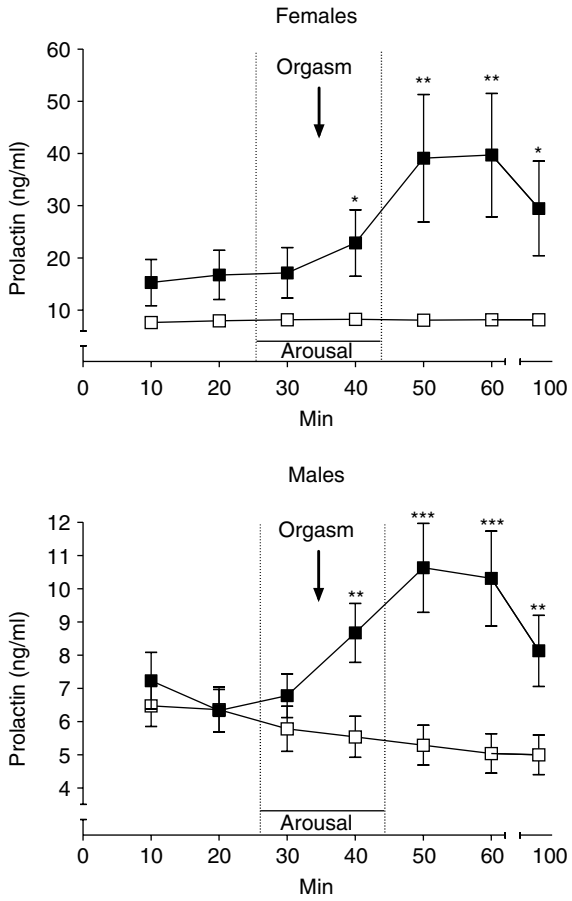

Figure 4 Effect of orgasm on peripheral PRL concentrations in human males and females before, during, and after sexual intercourse (filled squares) and during a control session (open squares). *$P<0.05$; **$P<0.01$; ***$P<0.001$. Reproduced, with permission, from **Exton MS, Kruger TH, Koch M, Paulson E, Knapp W, Hartmann U & Schedlowski M** 2001 Coitus-induced orgasm stimulates prolactin secretion in healthy subjects. *Psychoneuroendocrinology* **26** 287–294. © 2001 Elsevier Science Ltd.

ASES in the high PRL condition. Restored PRL levels were induced by administration of both drugs that led to an adjustment of effects. The inhibitory effects of PRL on sexual appetence in humans are well known from chronic hyperprolactinemia, which can be observed physiologically during lactation and pregnancy, as a side effect of various pharmacological treatments and in causes of prolactinoma. Pharmacological treatment of chronic hyperprolactinemia as a causal factor of sexual dysfunction is well established (Gillam *et al*. 2006). Nevertheless, a putative feedback of PRL to dopaminergic populations in humans, as mentioned above, deserves further investigation. So far, the PRL-induced changes in DA turnover for these regions have been examined by only a small number of studies, and the role of inhibiting or promoting dopaminergic activity does not always seem to be clear (for review, see Kruger *et al*. (2002, 2005)). However, PRL-responsive neurons in specific hypothalamic nuclei and the feedback of PRL on TIDA neurons have been characterized more intensively. This also included the medial preoptic area, the PVN, and limbic structures which are all of specific importance for sexual drive and function (Bakowska & Morrell 1997, Brown *et al*. 2010).

Implantation

PRL seems to play an important role in implantation and subsequent placentation in the human endometrium (Jabbour *et al*. 1998, Jones *et al*. 1998, Jabbour & Critchley 2001). Animal models and experimental studies suggest that paracrine PRL signaling plays a role in decidualization and embryo implantation (Garzia *et al*. 2004). In the human endometrium, PRLR protein can be immunolocalized to the glandular epithelium and a subset of stromal cells from the mid- to late secretory phase, as well as in early decidua (Jabbour *et al*. 1998, Jones *et al*. 1998, Gubbay *et al*. 2002). *PRLR* transcripts were also detected from the late secretory phase and first trimester decidua (Jones *et al*. 1998). Progesterone stimulates the production of PRLR when stromal cells transform into decidual cells (Tseng & Mazella 1999). PRL is recognized as a crucial signal for the initiation and maintenance of decidualization (Qiu *et al*. 2002). Lack of endometrial PRL during the implantation window seems to be involved in reproductive failure (Garzia *et al*. 2004). In the event of pregnancy, local expression and secretion of PRL persist until term (Jabbour & Critchley 2001). PRL enhances endometrial cell growth at low concentrations and inhibits it at high concentrations (Tseng & Mazella 1999).

The fact that PRL release may be disturbed in overweight patients (Rasmussen & Kjolhede 2004) and that these patients have increased difficulties in conceiving (Norman & Clark 1998) further supports the proposed role of PRL in conception and early pregnancy.

Beside hormonal influences, immune functions play an important role in the initiation of a successful pregnancy. PRL, in addition to its endocrine influence on the immune system, acts as a cytokine released within the immune system regulating lymphogenic responses (Matera 1996, Clevenger *et al*. 1998). Moreover, it has been shown that stress in early pregnancy is able to diminish the secretion of progesterone and PRL, which in turn may alter the pregnancy protective cytokine and immune cell milieu (Arck *et al*. 2008, Parker & Douglas 2010). Immunoreactivity of PRLR in a subset of stromal cells may be evidence of paracrine interaction between decidualized cells or of an immunoregulatory role for PRL (Jones *et al*. 1998).

PRL also exerts effects on the immune system, potentiating T-cell growth in response to various stimuli (Athreya *et al*. 1994). These effects are felt to be mediated by PRLR present on lymphocytes (Athreya *et al*. 1994).

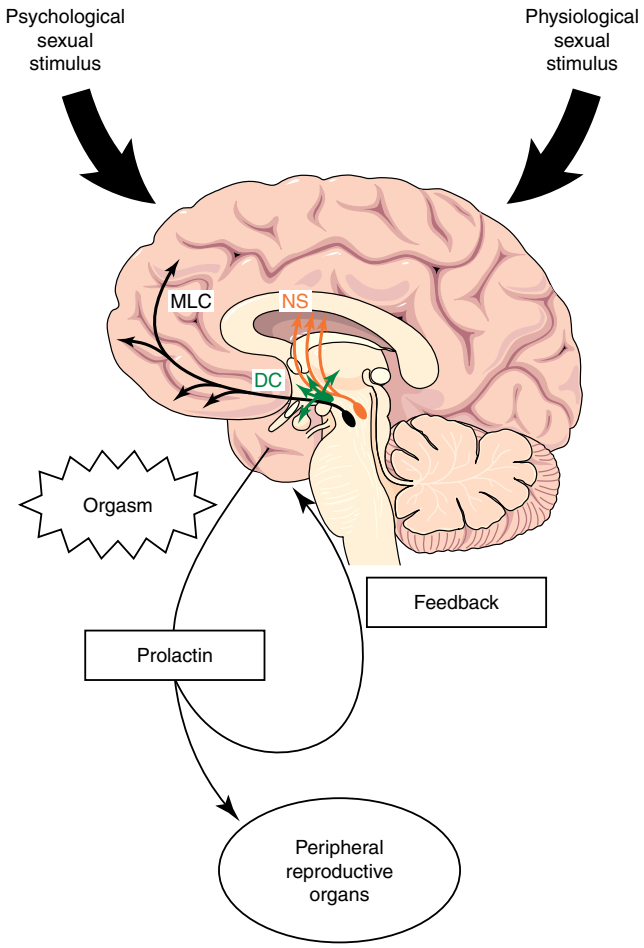

Figure 5 Theoretical model of the impact of PRL secretion following orgasm. PRL may influence peripheral reproductive organs, and/or may feedback to dopaminergic systems in the CNS recognized as playing an important role in the regulation of sexual behavior. DC, diencephalic neurons; MLC, mesolimbocortical neurons; NS, nigrostriatal neurons. Reproduced, with permission, from **Kruger TH, Haake P, Hartmann U, Schedlowski M & Exton MS** 2002 Orgasm-induced prolactin secretion: feedback control of sexual drive? *Neuroscience and Biobehavioral Reviews* **26** 31–44. © 2002 Elsevier Science Ltd.

Lymphocyte PRL levels vary up to tenfold throughout the menstrual cycle (Athreya *et al.* 1994). Also, PRLR is expressed in uterine CD56(+) NK cells, and ERK1 and ERK2 of purified uterine CD56(+) NK cells are phosphorylated in response to PRL (Gubbay *et al.* 2002). Consequently, PRL also seems to exert an effect on immunological mechanisms involved in menstrual cycle, implantation, and early pregnancy.

Pregnancy

High levels of circulating PRL during human pregnancy are well established, and were described for the first time in the early 1970s (Hwang *et al.* 1971, Jacobs *et al.* 1972, L'Hermite & Robyn 1972). Studies have shown that peak values reach more than five times the normal values at the 20–25th week of gestation (100–250 ng/ml; Boyar *et al.* 1975, Ben-Jonathan *et al.* 1996). Nevertheless, investigations on the PRL secretory pattern conducted on pregnant women in their early pregnancy showed that the values were already elevated at gestational week 10 (Boyar *et al.* 1975). De Hertogh *et al.* (1975) speculated that PRL concentration may even begin to rise at the third week of gestation. But so far, the precise onset of the PRL increase has not been established.

It is still controversial whether PRL is needed for the successful initialization of pregnancy in humans as it is in rodents. Falk (1992) presented a case in which a woman who had immeasurable serum PRL levels (<0.1 μg/l) and lifelong oligomenorrhea was able to conceive twice after ovulation induction (by clomiphene citrate) and had normal deliveries. In addition, Kauppila *et al.* (1987) reported that a patient with serum levels of <2 ng PRL/ml, severe menstrual cycle irregularities, and puerperal alactogenesis was able to conceive (without ovulation-inducing medication) and has two normal pregnancies. These two cases of normal conception and pregnancies without luteal phase support seem to suggest that not even minimum levels of PRL are necessary for ovulatory function. Nevertheless, there are several facts contradicting this suggestion: Gu (1993) demonstrated that the concentration of serum PRL showed a marked decrease in patients with spontaneous abortion compared to that of women who went to term. Recurrent spontaneous abortion has been associated with abnormal PRL levels (Bussen *et al.* 1999), and miscarriages are often related to significantly elevated PRL serum values (Hirahara *et al.* 1998). Furthermore, higher probability of luteal phase disturbances and infertility in women showing reduced postovulatory serum PRL levels (Kauppila *et al.* 1988) additionally strengthen the concept of PRL involvement in the regulation of the human corpus luteum. The positive outcome in the two case studies mentioned above could be explained by the theory of Schwarzler *et al.* (1997). They propose that PRL could also be involved in intraovarian regulation, which would (partially) compensate for the absence of endocrine support.

Similarities in and differences between PRL secretion in animal and human reproduction

When illustrating basic mechanisms of PRL secretion and the possible relevance for reproduction in animals and humans, similarities and differences become evident (Pfaus 1996, Pfaus *et al.* 2003, Ben-Jonathan *et al.* 2008). Before drawing the conclusion that the mating- or intercourse-induced PRL surge is important for initialization of early pregnancy in both species, these differences and similarities deserve further attention.

Regarding PRL production, this is restricted mainly to the pituitary in most animals, whereas in humans, it is also produced by numerous extrapituitary sites where it is regulated by local factors and predominantly acts a cytokine (Ben-Jonathan *et al*. 1996). This means that even in cases of severe pituitary insufficiency, local PRL production might be enough to maintain specific local functions including reproductive aspects. Consequently, a transfer from animal models to human ones is difficult for this aspect of PRL physiology.

The regulation of PRL release has been extensively studied in rodents and includes a series of releasing and inhibiting factors (for an overview, see for example Ben-Jonathan *et al*. (2008)). In contrast, the situation in humans seems to be less complex with a prominent role for DA as an inhibiting factor and (to a lesser extent) TRH as a releasing factor (Kruger *et al*. 2003*b*). On the reproductive level, we have outlined that PRL is critical in ovarian and other specific reproductive function of both rodents and humans, with a more convincing data basis for the animal models. Secretion patterns throughout the menstrual cycle have a particular pattern in rats with a peak during the afternoon of proestrus, whereas in human females, there is only a slight increase in PRL during the luteal phase. Other endocrine variables such as LH, estradiol, and progesterone show a comparable secretory profile in the two species.

Mating- or sexual intercourse-induced PRL secretion seems to be similar in rodents and humans (Kamel *et al*. 1975, Kruger *et al*. 1998, Exton *et al*. 1999). In addition, in rats, a specific release pattern is switched on after mating with PRL surges during early morning and late afternoon as outlined above (Bertram *et al*. 2006, Egli *et al*. 2006). This pattern continues during the first half of pregnancy (10–11 days) before placenta lactogen levels rise. Afterwards, PRL levels again increase on the day before parturition. In contrast, in humans, PRL is chronically elevated during pregnancy from week 6 to 8 of gestation and does not show the kind of rhythmic release pattern seen in rats. However, preliminary data by our own research group might indicate an altered PRL secretion pattern after sexual intercourse with a nocturnal as well as a diurnal PRL surge during a 24 h analysis comparable to the situation in the rat studies (study in progress). Consequently, there might be some overlap in human and rat physiology during this interval of pregnancy. If this preliminary observation in humans is further validated, consequent studies on the significance of such a PRL secretory pattern will be of interest.

In rodents, the luteotropic activity of PRL involved in the maintenance of corpus luteum makes it a mandatory factor for successful pregnancy (Bachelot & Binart 2007, Ben-Jonathan *et al*. 2008). Although in humans, hypo- as well as hyperprolactinemia may cause luteal function deficiency, serum PRL is not so crucial for corpus luteum function and consequently not for pregnancy either. However, although PRL seems not to be as important for this aspect of reproduction, there is a dramatic increase in PRL during human pregnancy that deserves further research with particular attention on implantation, immune function, fetal growth, and parturition. As mentioned above, local secretion of PRL, which is almost unique to humans, probably has specific functions for steroidogenesis, ovulation, fertilization, implantation, placentation, as well as the prevention of immune rejection of the pregnancy; however, the underlying pathophysiological aspects remain to be elucidated. Finally, the most prominent similarities between the two species seem to lie in lactational regulation by PRL.

Conclusion and outlook

All these facts together support the hypothesis that the PRL surge induced by sexual activity is important for the successful initialization of animal and, presumably, human pregnancy too – at least to a certain degree. According to the animal studies and mathematical models, we assume that the pronounced PRL surge triggered by sexual contact causes a disturbance in the PRL–DA–oxytocin balance of the hypothalamic and pituitary system that, in turn, leads to a significant change in the PRL secretory pattern.

Combining experimental and mathematical approaches, these kinds of studies may be an initial step in designing and establishing a virtual neuroendocrinological system for humans. A joint clinical and mathematical trial is currently in process, which is designed to verify the core principles of the animal model in humans and to dissect the role of PRL for conception and pregnancy in females.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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