Regulation of prolactin secretion by oestrogens: physiological and pathological significance

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Introduction

Prolactin is unique among the anterior pituitary hormones in that it is under tonic inhibitory control by the hypothalamus. There is much evidence that the major prolactin inhibitory factor is dopamine [1-3]. However, there are a number of physiological stimuli of prolactin secretion which can ‘override’ the effect of dopamine and one of the most important of these is oestrogen. Oestrogens are known to be involved in the physiological control of prolactin secretion in both rodent and primate [2, 4]. Furthermore, exogenous oestrogens have long been known to induce prolactin-secreting pituitary tumours in certain strains of rat [5-7]. In recent years there has been a resurgence of interest in the physiological and pathophysiological actions of oestrogen on prolactin secretion. This research has been prompted by the recognition that pathological hyperprolactinaemia (often associated with the presence of a pituitary tumour) presenting with disturbances in the menstrual cycle, is a common finding in women of reproductive age [8], thus raising the question of a role for endogenous oestrogens in the aetiology of hyperprolactinaemia. In the following pages I shall review the evidence for involvement of oestrogens in the physiological control of prolactin secretion, highlight recent studies bearing on the mechanism of oestrogen action on prolactin and discuss the implications of the effects of endogenous and exogenous oestrogens in the aetiology of hyperprolactinaemia in man.

Physiological regulation of prolactin secretion by oestrogen

The importance of endogenous oestrogen in the physiological control of prolactin secretion was first delineated in the rat and has been reviewed by Neill [2]. Prolactin concentrations in the plasma are low before the onset of the first oestrus cycle; after puberty they remain low during the cycle until the afternoon of pro-oestrus when there is a 10-fold increase in levels [9]. This ‘surge’ in prolactin is similar to that observed for luteinizing hormone (LH) and is preceded by a rapid increase in serum oestradiol concentrations. The pro-oestrus ‘surge’ of prolactin can be prevented by pre-treatment with an antiserum to oestradiol [10], thereby indicating that this dramatic rise in prolactin (which, in the rat, is important in the maintenance of the corpus luteum) is, indeed, oestrogen dependent. Oestrogen also appears to affect ‘non-surge’ levels of prolactin in that these low basal concentrations fall significantly lower after ovariectomy [11] (to levels comparable with those of male rats), but can be restored by the administration of oestradiol.

More recently, studies in man have confirmed the importance of oestrogen as a physiological prolactin-stimulating agent, although cyclical changes in prolactin levels are less clear-cut than in the rodent. Differences in basal prolactin concentrations between men and women are small and, in most studies, not statistically significant [12]. However, the prolactin response to exogenous thyrotrophin-releasing hormone is significantly greater in women than in men or prepubertal children [12]. There remains some controversy regarding changes in serum prolactin concentrations during the menstrual cycle [13]. Some studies have shown no significant changes throughout the cycle [14-16] whilst others have demonstrated that prolactin levels are higher at the time of the mid-cycle surge of LH than in the early follicular phase [13, 17, 18]. Because of the episodic nature of prolactin secretion these discrepancies may simply be related to the frequency of blood sampling [13]. Prolactin concentrations increase significantly during pregnancy to reach levels in the third...
Mechanism of oestrogen-induced prolactin secretion

Exposure to endogenous oestrogen (e.g. during pregnancy) or to exogenous treatment is associated with increased synthesis and release of prolactin [24] and, in the long term, with an increase in the number of pituitary lactotrophs [25]. There are, however, at least three mechanisms by which oestrogens can stimulate prolactin secretion: (i) a direct effect on the pituitary, (ii) modulation of hypothalamic inhibitory or stimulatory factors, and (iii) alteration of pituitary responsiveness to prolactin-regulating factors. There is evidence that each mechanism may have some part to play in both normal and excessive secretion of prolactin but the relative importance of these various mechanisms remains to be determined.

(1) Direct stimulation of the lactotroph by oestrogen

The most persuasive evidence for a direct action of oestrogen at pituitary level is (a) the ability of oestrogen in vitro to stimulate prolactin secretion by incubated anterior pituitary tissue [26], and (b) the lactogenic effect of oestradiol implanted directly into the anterior pituitary of the rabbit [27]. Recent work in the sheep shows that prolactin synthesis induced by oestradiol treatment either in vivo [28] or, significantly, in pituitary cell culture [29] is associated with increased activity of messenger RNA for the presumed precursor for prolactin (preprolactin mRNA).

(2) Modulation of hypothalamic prolactin-inhibitory or-stimulatory factors by oestrogen

Porter and co-workers have demonstrated that there is a reduction of dopamine release into hypothalamic portal vessels during pro-oestrus [30]; this can be mimicked by short-term treatment of ovariectomized animals with exogenous oestrogen [31]. These observations are consistent with the hypothesis that reduction in hypothalamic dopamine release may mediate the effect of oestrogen on prolactin secretion. However, the results of longer term exposure to oestrogen appear to contradict this evidence in that such treatment is associated with an increase in dopamine turnover [32] and dopamine release into the portal vessels [33]. One possible explanation for this discrepancy is that the prolonged hyperprolactinaemia produced by chronic treatment will itself lead to an increase in dopamine turnover by activation of a well-described short-loop feedback between lactotroph and hypothalamus [2]. This is borne out by the finding that the increase in dopamine turnover induced by this form of oestrogen treatment can be prevented by hypophysectomy [34].

Clearly oestrogen could also act by stimulation of hypothalamic prolactin-releasing factors [35]. There is little direct evidence for this but one candidate for a physiological prolactin-releasing factor (PRF) is thyrotrophin-releasing hormone (TRH), and a recent study in our laboratory suggests that physiological doses of oestrogen may stimulate hypothalamic TRH release (H. D. Mason, M. C. Sheppard, K. I. J. Shennan & S. Franks, unpublished work).

(3) Alteration of pituitary responsiveness to prolactin-regulating factors

Oestradiol can act directly on the pituitary to impair the response of the lactotroph to dopamine. Studies using short-term incubation or culture of rat anterior pituitary tissue indicate that the inhibitory effect of dopamine can be partially reversed by pre-treatment with oestrogen in vivo or in vitro [36, 37]. However, there is doubt about whether this has any bearing on regulation of prolactin in man, since oestradiol treatment of hypogonadal women appears to enhance rather than block dopamine-induced suppression of prolactin [38]. It is well recognized that oestrogen increases the response of prolactin to administration of TRH in several species, including man [39-41], and it is therefore reasonable to suppose that this is applicable to endogenous TRH. There seems little doubt that the effect is a direct one on the lactotroph [42]; the mechanism is unclear but it has been suggested that oestrogen increases the number of TRH receptors on the pituitary [43]. Oestrogen may also affect the response to other proposed prolactin-releasing factors. Under certain conditions gonadotrophin-releasing hormone (GnRH) has been shown to stimulate the release of prolactin as well as gonadotrophin [44, 45]. The prolactin response to GnRH can be induced or amplified by oestrogen treatment of hypogonadal or normal men [46].
Catechol oestrogens and prolactin

The catechol oestrogens are quantitatively important ring A hydroxylated intermediary metabolites of primary oestrogens. The presence of these 2- and 4-hydroxy oestrogens (called 'catechol oestrogens' because adjacent hydroxy groups at the 2,3 or 3,4 positions on the phenolic A-ring resemble the structure of other catechol derivatives) has been recognized for many years, but until recently they were regarded as biologically inert metabolites. However, recent work has demonstrated that these compounds, which can be synthesized in hypothalamus and pituitary, may have significant effects on the secretion of prolactin and gonadotrophins [47-49]. For the most part the actions of 2- and 4-hydroxyoestrogens resemble that of weak oestrogens (i.e. they are similar to that of the parent oestrogen: oestradiol) and these are consistent with their known oestrogen receptor-binding kinetics [49, 50]. However, there are certain effects of 2-hydroxylated oestrogens which cannot be explained on the basis of an 'oestrogenic' action.

Intravenous infusion of 2-hydroxyoestrone (quantitatively the most important catechol oestrogen in man) has been shown to lower serum prolactin levels in normal women [51] (although it must be said that further studies from other laboratories on normal [52] or hyperprolactinaemic [53] patients have been unable to confirm this). Linton and colleagues, working on rat pituitary tissue in vitro, have shown that 2-hydroxyestradiol, in low doses, can rapidly suppress prolactin secretion in a manner which resembles that of dopamine [54]. The mechanism and physiological significance of this intriguing phenomenon remains unexplained but these findings have since been confirmed in other laboratories (S. Franks & H. Mason, unpublished results; S. J. Lamberts, personal communication).

Role of oestrogen in pathological hyperprolactinaemia

It has been known for nearly 50 years that the administration of large doses of oestrogen (in early studies this was in the form of a crude ovarian extract) may lead to lactotroph hyperplasia and, in some species of rat, to frank pituitary tumours [5-7]. More modern work has confirmed that these are induced prolactin-secreting tumours [24]. Although many of the cellular mechanisms mediating oestrogen-induced prolactin secretion have been defined it is still not clear why some species develop tumours and others simply show lactotrophi hyperplasia. The relevance of findings in the rat to the aetiology and growth of prolactinomas in man remains uncertain. Exogenous oestrogens may cause hyperprolactinaemia in men and women; prolactin secretion increases and the pituitary enlarges during pregnancy. It is therefore important to address the following questions: (i) can exogenous oestrogen, particularly as contained in the oral contraceptive, be implicated in the cause of prolactinomas in women?; (ii) could abnormalities of endogenous oestrogen secretion lead to the development of a tumour?; (iii) can oestrogens, endogenous or exogenous, influence the growth of established pituitary prolactinomas?

(i) Pharmacological doses of oestrogen increase serum prolactin levels in man [55, 56] and several studies have indicated that oral contraceptive treatment is also associated with elevation of serum prolactin concentrations [57-59]. However, the changes induced by the widely used preparations containing 30 µg of 50 µg of ethinyloestradiol or mestranol, combined with a progestogen, are small and in many patients prolactin levels remain within the normal range [59]. Patients with hyperprolactinaemia (with or without a pituitary tumour) frequently give a history of oral contraceptive use but there is no evidence that this is causally related to the elevation of prolactin in these women [59]. This has been clearly shown in case-control [60, 61] retrospective [62] and prospective [63] studies. The absence of a clear association between oral contraceptive use and hyperprolactinaemia is reassuring, if, perhaps, rather unexpected. It is possible that the progestogen component of the pill is exerting a 'protective' effect against that of oestrogen [64].

(ii) It remains possible that abnormalities of endogenous oestrogen production or metabolism are related to the aetiology of prolactinomas but this is difficult to assess in established cases of hyperprolactinaemia since elevated prolactin levels, in turn, induce oestrogen deficiency [65].

(iii) There is little doubt that untreated prolactinomas can enlarge during pregnancy as a result of the increase in endogenous oestrogens in maternal plasma. This phenomenon has led to serious neurological complications in a significant number of patients [66]. Ovulation was induced by a variety of methods (but principally by exogenous gonadotrophins) in these women and recent data from bromocriptine-induced pregnancies in women with prolactinomas shows that the risk of serious complications may be much less in this treatment group [67]. There is little evidence that oral contraceptive treatment of hyperprolactinaemic women promotes tumour growth. Again, the key factors may be the low dose of oestrogen and the 'protective' effect of progestagen.
Conclusion

The importance of oestrogens in the physiological regulation of prolactin secretion in many species, including man, has been clearly established. Among the possible mechanisms of action of oestrogen on the lactotroph the most important seems to be a direct effect mediated by binding to a cytosol receptor in the lactotroph and translocation of the hormone–receptor complex to the nucleus (leading to stimulation of prolactin synthesis and release). However, modulation of the secretion or receptor in the lactotroph and translocation of oestrogen, 2-hydroxyoestradiol, causes rapid involvement and the relative importance of these mechanisms remains to be determined. The catechol oestrogen, 2-hydroxyoestradiol, causes rapid suppression of prolactin (at least, in vitro) at a concentration which suggests this effect might be of physiological significance. Further studies are required to explore this phenomenon but it is an attractive hypothesis that the action of oestradiol in the lactotroph may be modulated by the degree of conversion into a metabolite which has the opposite effect to its parent oestrogen on the secretion of prolactin. Since the 2-hydroxylase enzyme system appears to be affected by a number of hypothalamic and pituitary peptides (including prolactin itself) [68, 69], this pathway could prove to be important in the final expression of oestriadiol action on the lactotroph.

The role of oestrogen in the aetiology of hyperprolactinaemia in women is still uncertain. Despite the prevalence of prolactinomas in women of reproductive age, it is difficult to obtain evidence that either oral contraceptive treatment or changes in endogenous oestrogen are directly implicated in the genesis of this disorder. It remains possible and plausible that endogenous abnormalities in production or processing of oestrogen play a part in causing prolactin-secreting tumours and, not surprisingly, this is currently an active area of research.

References


