

Disorders of prolactin secretion

M. O. THORNER

From the Department of Endocrinology, St Bartholomew's Hospital, London EC1A 7BE

Prolactin was not identified as a distinct hormone separate from growth hormone until 1970 (Frantz and Kleinberg, 1970; Forsyth and Myres, 1971; Forsyth *et al.*, 1971). It was the last of the currently recognised anterior pituitary hormones to be isolated, the reason being that it has great physicochemical, immunological, and biological similarities to growth hormone, the amount of which in the pituitary greatly exceeds that of prolactin. In lower vertebrate species prolactin is important for a wide variety of metabolic processes but in man it seems to be important only in the control of lactation and reproduction (Nicoll, 1974). Its secretion is predominantly under tonic inhibition by the hypothalamus. Thus disorders of prolactin secretion are usually associated with hyperprolactinaemia. Prolactin deficiency is very rare and is usually associated with panhypopituitarism—for example, Sheehan's syndrome.

Mechanism of control of prolactin secretion

Prolactin is unique among the anterior pituitary hormones in that its secretion is under tonic inhibitory control. The hypothalamus secretes a prolactin release-inhibiting factor which is secreted into the portal capillaries and thus transported to the anterior pituitary.

The nature of the prolactin release-inhibiting factor (PIF) has been the subject of dispute. Initially, it was believed that dopamine stimulated the release by the hypothalamus of a peptide substance (PIF). However, it is now almost certain that dopamine itself is the major physiological PIF. The evidence for this consists of data derived from *in-vitro* culture of pituitary cells. Pasteels (1961, 1963) showed that prolactin release could be inhibited by incubating the pituitary *in vitro* with hypothalamic extracts. Later MacLeod showed that prolactin release could also be inhibited by incubating the pituitary with noradrenaline and dopamine (MacLeod *et al.*, 1969; MacLeod *et al.*, 1970). Furthermore, dopamine receptors are found on prolactin-secreting cells (Kimura and MacLeod, 1975).

Not only does dopamine inhibit prolactin secretion but this effect may be blocked by preincubating the

tissue with dopamine receptor-blocking drugs (MacLeod and Lehmeyer, 1974). Schally and his colleagues, in trying to isolate PIF, extracted 500 000 pig hypothalami and found that their most potent fraction contained only the catecholamines dopamine and noradrenaline (Schally *et al.*, 1976). Shaar and Clemens (1974) suggested that all the PIF activity in the hypothalamus may be accounted for by its dopamine content alone since most of the PIF activity can be extracted with alumina. Possibly there are other PIFs which are non-catecholamine in nature and whose effects are not blocked by dopamine receptor-blocking drugs (Dupont and Redding, 1975).

PROLACTIN RELEASING FACTOR (PRF) In birds prolactin is under tonic stimulation by the hypothalamus. Although in man the predominant control mechanism is inhibitory there is probably also a PRF. Shortly after the isolation and synthesis of thyrotrophin releasing hormone (TRH) it was found that it released prolactin as well as thyrotrophin, both *in vitro* and *in vivo* (Tashjian *et al.*, 1971; Bowers *et al.*, 1971; Jacobs *et al.*, 1971; Noel *et al.*, 1974). The significance of this observation is not clear since in physiological circumstances TSH is not secreted with prolactin—for example during suckling (Gautvik *et al.*, 1974).

There are also reports of the existence of a PRF distinct from TRH (Labella *et al.*, 1972; Valverde *et al.*, 1972; Frohman and Szabo, 1975).

Prolactin secretion in man

Prolactin levels in the fetus rise progressively until birth, after which they fall to prepubertal levels over the first one to two months (Aubert *et al.*, 1975). Prolactin levels during the reproductive years of life are higher in normal women than in men, although there is a large overlap between them. There is a small rise of prolactin in girls at puberty (Guyda and Friesen, 1973; Ehara *et al.*, 1975; Aubert *et al.*, 1976).

Prolactin levels also rise during pregnancy, probably in response to the high oestrogen levels

In certain other primates, in whom the rise in oestrogen levels is only small, the rise in prolactin is very much smaller (Friesen *et al.*, 1972). Prolactin is also released during lactation, particularly when the baby feeds at the breast. This rise in plasma prolactin in response to suckling is maximal in the early postpartum period and then gradually diminishes, accompanied by a fall in the basal prolactin levels to normal (Noel *et al.*, 1974).

There is a circadian rhythm of prolactin secretion with a rise related to sleep (Nokin *et al.*, 1972; Sassin *et al.*, 1972; Parker *et al.*, 1973). It has been suggested that there is a small mid-cycle surge in prolactin secretion and a secondary rise in the luteal phase (Robyn *et al.*, 1973), but others have not been able to confirm this observation (Robyn *et al.*, 1977).

Prolactin is secreted in a pulsatile fashion and blood levels fluctuate considerably at intervals of only a few minutes (Parker *et al.*, 1973). It is also released in response to both physical and emotional stress (Noel *et al.*, 1972).

Clinical significance of hyperprolactinaemia

A physiological 'hyperprolactinaemia' occurs during postpartum lactation. This is associated with a delay in the resumption of cyclical ovarian function in spite of the return of normal gonadotrophin secretion (Reyes *et al.*, 1972; Bonnar *et al.*, 1975). In western society, where women are well nourished and breast feeds supplemented, the rise in prolactin levels in response to breast feeding is maintained for only about three months. But in more primitive societies in which breast feeding is prolonged prolactin levels remain raised for much longer and gonadal function may be inhibited for one or two years (Robyn *et al.*, 1977).

Hyperprolactinaemia is a common cause of gonadal dysfunction, particularly in women. Its incidence in women with secondary amenorrhoea varies from 13% to over 30% (Franks *et al.*, 1975; Seppälä *et al.*, 1975; Bohnet *et al.*, 1976). Most patients with hypogonadism due to pituitary tumours do not in fact suffer from gonadotrophin deficiency, they suffer from hyperprolactinaemia. Only about 30% of patients with hyperprolactinaemia have galactorrhoea.

Causes of hyperprolactinaemia

A common cause of hyperprolactinaemia is the administration of drugs which raise prolactin levels. These are of three main classes: (1) dopamine receptor blocking drugs—for example, phenothiazines, butyrophenones, and benzamides (for

example, metoclopramide); (2) dopamine depleting drugs—for example, reserpine, alpha methyl dopa; and (3) drugs acting through non-dopaminergic mechanisms—for example, oestrogens and thyrotrophin-releasing hormone.

Hyperprolactinaemia often occurs in patients with pituitary tumours and may occur in patients with hypothalamic disease or any disease affecting the pituitary stalk. Rarely hyperprolactinaemia may result from primary hypothyroidism. In that case replacement therapy with thyroid hormone may restore prolactin levels to normal (Edwards *et al.*, 1971). In some patients no cause for hyperprolactinaemia can be found.

Women with hyperprolactinaemia may present in a variety of ways—with secondary amenorrhoea or any menstrual abnormality, oligomenorrhoea, polymenorrhoea, or even with a normal menstrual cycle. It has been suggested that women with hyperprolactinaemia who present with infertility and have a normal cycle may be suffering from defective luteal function (Del Pozo *et al.*, 1977).

Galactorrhoea often accompanies the amenorrhoea related to the cessation of oral contraceptives. This is sometimes associated with raised prolactin levels, and it is not clear whether it is due to the contraceptive or whether galactorrhoea is induced only in patients who were already hyperprolactinaemic before taking the oral contraceptive (Besser *et al.*, 1972; Thorner *et al.*, 1974; Tyson *et al.*, 1975).

Hyperprolactinaemia in men

Hyperprolactinaemia is less common in men than in women, but may lead to hypogonadism with absolute or relative impotence which is sometimes associated with loss of libido. Gynaecomastia is not a feature of the syndrome and galactorrhoea occurs in only 30% of cases. The testes are usually normal on examination but may sometimes be unusually soft (Besser *et al.*, 1972; Thorner *et al.*, 1974; Thorner and Besser, 1977). The sperm count and morphology are usually normal.

Hyperprolactinaemia and pituitary tumours

Hyperprolactinaemia is often associated with a small pituitary tumour or microadenoma. There is no general agreement on the criteria for such a diagnosis. Most workers are strongly influenced by the basal level of prolactin. Frantz *et al.* (1973) believe that a prolactin level above 200 $\mu\text{g/l}$ (their normal range being up to 50 $\mu\text{g/l}$) suggests a pituitary tumour. The other criterion that should be considered is the appearance of the pituitary fossa on a skull

radiograph. Often there are only very subtle changes, so first-class neuroradiology is needed. The skull x-ray abnormalities and the follow-up at surgery have been discussed by Vezina and Sutton (1974).

Clearly a microadenoma in a woman requires treatment in its own right, particularly if the patient wishes to become pregnant. Some centres practise transphenoidal removal of the microadenoma while others, including our own, use external pituitary irradiation. Assessment of the visual fields is very important. Patients with a visual field defect will require air encephalography and if there is suprasellar extension they will require surgery.

Medical treatment of hyperprolactinaemia

Drugs which stimulate dopamine receptors lower prolactin levels and act as functional analogues of the naturally occurring PIF, dopamine. The greatest experience has been gained with the semi-synthetic ergot alkaloid bromocriptine, 2-brom-alpha-ergocryptine. This drug was developed specifically to inhibit prolactin secretion and does not have the oxytocic and cardiovascular effects of the parent compound. It usually causes a rapid fall of prolactin levels to normal (Fig. 1).

To avoid side effects the starting dose of bromocriptine should be low and taken at bed time. Usually 1.25 or 2.5 mg is taken for three days and this is increased by 1.25 or 2.5 mg every three or four days in divided doses until the usually effective dose of 7.5 mg is attained.

Over the past five years we have treated 44 women

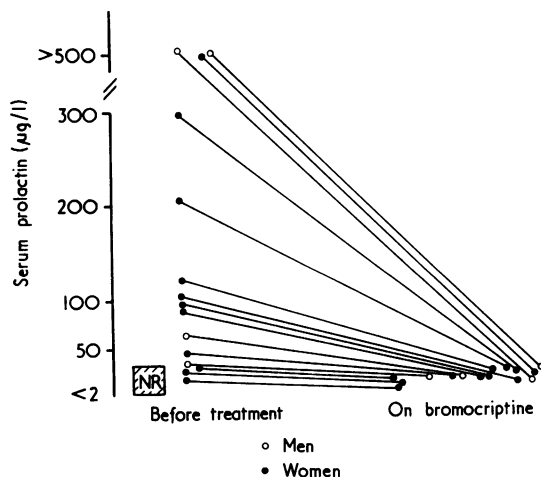


Fig. 1 Changes in circulating prolactin levels in a group of patients with galactorrhoea-hypogonadism syndrome treated with bromocriptine. NR = normal range. From Besser and Thorner (1975) with kind permission of the Editor of the Postgraduate Medical Journal.

and 25 men for hyperprolactinaemia with bromocriptine. In most cases prolactin levels have fallen to normal and galactorrhoea has ceased or improved usually within the first few weeks. In most women cyclical ovarian function has resumed within six weeks, although it may take up to nine months. The time taken for the resumption of menstruation is shown in Fig. 2.

Bromocriptine and pregnancy

Some 231 pregnancies have now been recorded in women treated for infertility with bromocriptine. There is no evidence of teratogenicity associated with the drug. Nevertheless, women should stop treatment as soon as pregnancy is suspected (Thorner *et al.* 1975; Thorner and Besser, 1977).

Experience with exogenous gonadotrophin therapy for infertility has shown that there is a small risk of visual field defects developing during pregnancy, particularly in patients with pituitary tumours. Erdheim and Stumme (1909) showed that during pregnancy the number of 'pregnancy' cells in the pituitary increased and that the volume and weight of the gland increased. The volume increased further with each pregnancy. However, suprasellar extension sufficient to cause visual field defects was not found at necropsy in any of the patients who died. It therefore seems that only patients with pre-existing pituitary tumours are at risk. But, as already stated a pituitary tumour, particularly a microadenoma may be difficult to diagnose.

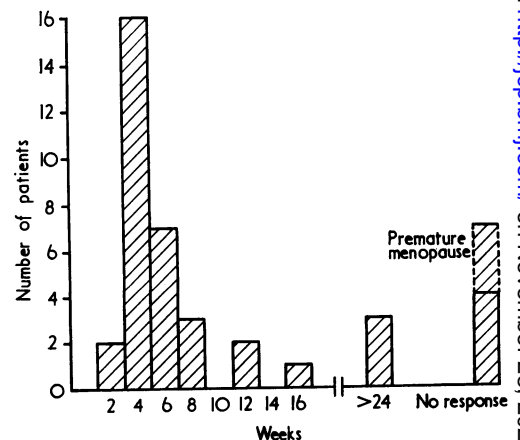


Fig. 2 Time taken for resumption of normal menstruation and ovulation in 42 women with hyperprolactinaemia and gonadal dysfunction treated with bromocriptine. Those who did not respond included 3 shown by ovarian biopsy to have had a premature menopause. From Thorner and Besser (1977) with kind permission of the publishers (Academic Press).

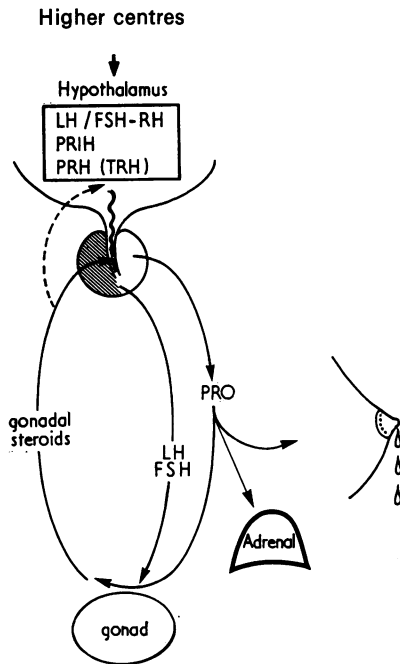


Fig. 3 Diagrammatic representation of prolactin-induced blockade of the actions of the gonadotrophins (LH and FSH) on the gonad and its other actions on the breast and adrenal cortex. PRO = prolactin; PRIH = prolactin release-inhibiting hormone (or factor); PRH (TRH) = prolactin releasing hormone (thyrotrophin releasing hormone). Note: TRH will release prolactin but probably it is not the physiological PRH. From Thorner and Besser (1977) with kind permission of the publishers (Academic Press).

Bromocriptine treatment in men

Lowering prolactin levels in men with bromocriptine leads to a resumption of normal gonadal function and a restoration of normal libido and potency (Besser *et al.*, 1972; Thorner *et al.*, 1974; Thorner and Besser, 1977; Thorner *et al.*, 1977).

Mechanism of hypogonadism in hyperprolactinaemia

The mechanism of hypogonadism in hyperprolactinaemia (Fig. 3) has not been fully elucidated. A central effect of hyperprolactinaemia on gonadotrophin secretion is suggested by the modification of pulsatile secretion, especially of LH (Boyer *et al.*, 1974; Bohnet *et al.*, 1976), and by the interference with feedback control (Glass *et al.*, 1975). However, an initial assumption that gonadotrophin secretion is deficient has not been borne out by our experience, since our hyperprolactinaemic patients have normal gonado-

trophin levels and a normal or even exaggerated response to GnRH (Mortimer *et al.*, 1973; Thorner *et al.*, 1974; Child *et al.*, 1975). There is also the possibility that prolactin may in some way interfere with the action of the gonadotrophins on the gonads, in which case lowering the prolactin level should rapidly restore gonadal function to normal. In fact this does happen when prolactin levels are lowered in hyperprolactinaemic patients by bromocriptine. Cyclical function returns together with positive feedback by oestrogens (Bohnet *et al.* 1976).

There is other *in-vivo* and *in-vitro* evidence to suggest such an action. Thus McNatty *et al.* (1974) showed that human ovarian granulosa cells, taken at laparotomy and cultured *in vitro* in the presence of constant amounts of gonadotrophin, secrete progesterone in the presence of normal concentrations of prolactin. However, if the prolactin concentration in the medium is increased the amount of progesterone secreted is reduced. Similarly the response to HCG in men and to pergonal in women is less in the presence of hyperprolactinaemia.

Possibly prolactin may also have an effect on the adrenal and may alter steroidogenesis there, resulting in increased secretion of adrenal androgens which, in the female, may lead to the polycystic ovary syndrome. In this respect it is of interest that Forbes *et al.* (1954) noted in their now classic paper that the majority of patients with galactorrhoea had clinical features that we now associate with the polycystic ovary syndrome. Giusti *et al.* (1977) have found raised plasma levels of dehydroepiandrosterone sulphate in patients with hyperprolactinaemia. They fell to normal when prolactin levels were lowered.

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