New insights into human prolactin pathophysiology: genomics and beyond

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Purpose of review
To briefly summarize what is known regarding hyperprolactinemia and prolactin-secreting tumors, and review recent findings.

Recent findings
Prolactin was previously thought to inhibit secretion of gonadotropin-releasing hormone (GnRH) by directly inhibiting the firing of GnRH neurons, resulting in hypogonadotropic hypogonadism and infertility. However, kisspeptin has recently been implicated as the mediator of hyperprolactinemia-induced infertility, by acting upstream of the GnRH neurons as an integrator of endocrine signals.
Macroprolactin is generally considered to be inactive and clinically insignificant, but new studies have suggested that patients with macroprolactinemia may have reproductive manifestations as well as sexual dysfunction.
Several mutations and polymorphisms in the prolactin receptor have been described, which could describe a genetic cause for prolactinomas and characterize cases of isolated familial hyperprolactinemia.
Kisspeptin and tyrosine kinase inhibitors have emerged as potential new therapeutic targets for the treatment of hyperprolactinemia and dopamine-resistant prolactinomas.

Summary
Molecular studies are shedding light on the pathophysiology of hyperprolactinemia and the effects of excess prolactin production on the reproductive system. Similarly, genetic studies have begun to reveal how differences in prolactin receptor function may account for some of the previously 'idiopathic' cases of hyperprolactinemia and bring to light new causes of prolactinomas. Further elucidation of the transcriptional pathways affected by these genetic changes may help to create new therapeutic targets.

Keywords
hyperprolactinemia, kisspeptin, prolactin receptor variant, prolactinomas, tyrosine kinase inhibitors

INTRODUCTION

Prolactin is a hormone that is synthesized and secreted by lactotrope cells of the anterior pituitary. Prolactin is encoded by a single gene on chromosome 6 that contains 6 exons and 4 introns [1]. Multiple isoforms of prolactin exist, with the main isoform weighing 23 kDa [2]. Other isoforms, including the 14, 16, and 22 kDa prolactin variants, are generated by proteolytic cleavage of the 23 kDa protein. The prolactin receptor is a transmembrane receptor that is a member of the hematopoietic cytokine receptor superfamily. The structure of both prolactin and its receptor, and their downstream signaling pathways, has been reviewed extensively elsewhere (see [2,3]).

Prolactin is best known for its role in lactation and reproduction. However, prolactin receptors are ubiquitous throughout the human body, reflecting prolactin's diverse role in water and salt balance, growth and development, endocrinology and metabolism, brain and behavior, and immune regulation and protection [3]. More recently, prolactin has been implicated in glucose homeostasis, and has been shown to result in the proliferation of pancreatic beta cells [4–6]. Prolactin has also been shown to play a role in cartilage physiology, promoting cartilage survival and decreasing cartilage inflammation in certain inflammatory states [7,8].

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KEY POINTS

- Molecular studies are shedding light on the pathophysiology of hyperprolactinemia and the effects of excess prolactin production on the reproductive system.
- Similarly, genetic studies have begun to reveal how differences in prolactin receptor function may account for some of the previously 'idiopathic' cases of hyperprolactinemia and bring to light new causes of prolactinomas.
- Further elucidation of the transcriptional pathways affected by these genetic changes may help to create new therapeutic targets.

PHYSIOLOGY OF PROLACTIN SECRETION

Prolactin secretion is regulated by tuberoinfundibular dopamine (TIDA) neurons located in the arcuate nucleus, which release the inhibitory neurotransmitter dopamine [2]. When TIDA neurons are exposed to prolactin, the transcription factor STAT5 undergoes phosphorylation and stimulates dopamine secretion. This reaction is suppressed during lactation to permit physiological hyperprolactinemia. Dysregulation of this physiologic regulatory system results in pathologic hyperprolactinemia.

HYPERPROLACTINEMIA AND ITS EFFECTS ON REPRODUCTION

Hyperprolactinemia most commonly manifests as galactorrhea, amenorrhea, and infertility, but can also present with compressive symptoms, such as headache and visual effects. Until recently, the mechanism behind how hyperprolactinemia resulted in infertility was unclear. It was hypothesized that prolactin excess acted directly on GnRH neurons, resulting in decreased pulsatility and decreased GnRH, follicle-stimulating hormone (FSH) and luteinizing hormone secretion [9]. However, only a small proportion of GnRH neurons express the prolactin receptor, and studies have shown that membrane excitability of GnRH neurons is not affected by prolactin [9,10], suggesting a different mechanism of action. Newer studies have revealed a role for neurons expressing the *Kiss1* gene within the hypothalamus that secrete a neuropeptide called kisspeptin. Kisspeptin was initially described as a metastasis suppressor, but has been reported to act as a powerful activator of GnRH neurons [11]. Importantly, kisspeptin neurons have been shown to express prolactin receptors and are thus perfectly poised to act as an integrator of endocrine signals [12,13]. Several studies have shown that kisspeptin mRNA levels decrease in the rostral periventricular region of the third ventricle and arcuate nucleus in pregnant and lactating mice [14,15]. In-vitro experiments showed that kisspeptin neurons activated GnRH neurons in the control state, but not during lactation [14]. This appears to be a physiologic adaptation similar to the inhibition of dopamine release during lactation. However, adding the kisspeptin exogenously was shown to override this inhibition in the lactational state [14].

Similarly, a mouse model of hyperprolactinemia-induced hypogonadotropic anovulation also demonstrated decreased kisspeptin expression [16]. Administration of kisspeptin in these mice restored GnRH and gonadotropin secretion, as well as menstrual cyclicity [17]. Taken together, these results suggest that prolactin exerts its actions on kisspeptin neurons upstream of the GnRH neuron, rather than directly onto the GnRH neuron itself.

CAUSES OF HYPERPROLACTINEMIA

The causes of hyperprolactinemia can be placed into four categories: physiological, analytical, pathological, and idiopathic (Table 1 – adapted from [18]). Physiological causes of hyperprolactinemia include pregnancy, lactation, and nipple stimulation. This review intends to focus on new developments in each of the latter three categories.

Analytical hyperprolactinemia

Analytical causes of hyperprolactinemia include both the presence of 'big prolactin,' which is the dimer of the monomeric form of prolactin and 'big

Table 1. Main causes of hyperprolactinemia

Physiological
Pregnancy
Lactation
Nipple Stimulation
Analytical
Macroprolactinemia
Pathological
Prolactinomas and mixed secreting adenomas
Hypothalamic and pituitary stalk disorders
Medication
Chronic renal failure
Ectopic prolactin secretion
Genetic
Idiopathic
Unknown

Adapted from [18].

big prolactin,' which is a large complex of monomeric prolactin molecules and IgG antibodies [19]. Macroprolactinemia is a term that is used when the concentration of macroprolactin exceeds 60% of the total serum prolactin concentration, and is diagnosed using the Polyethylene glycol (PEG) precipitation method, which utilizes differential precipitation of proteins according to their molecular weight and solubility in defined concentrations of aqueous PEG solution [20–22].

Macroprolactinemia represents an under-recognized cause of elevated prolactin [20,23]. The reported prevalence of macroprolactinemia varies from study to study, with estimates varying between 8 and 66% of individuals with hyperprolactinemia [24▪▪]. Macroprolactin is not associated with pituitary adenomas and exhibits low biological activity as a consequence of its size, which results in diminished access to prolactin receptors within different tissues throughout the body, as well as a lack of inhibitory stimuli to the hypothalamus. Macroprolactinemia was previously thought to be asymptomatic, but one study reported up to 72.7% of patients had reproductive manifestations, including anovulatory infertility, menstrual irregularity, early abortions, implantation failure, and galactorrhea [24▪▪]. The hypothesis for this observed difference in phenotype was that the participants within this study had prolactin levels greater than 100 ng/ml, which is much higher than the inclusion criteria for other studies. Another study found that when compared with controls, women with elevated macroprolactin had higher scores on the *Beck Depression Inventory Second Edition* and Female Sexual Function Index, indicating more depressive symptoms and disturbances in sexual desire [25▪]. Further research is needed to elucidate why some patients are asymptomatic, whereas others suffer significant symptoms as a result of macroprolactinemia.

Pathological hyperprolactinemia

Pathological hyperprolactinemia can result from a variety of conditions, including pituitary adenomas, hypothalamic and pituitary stalk disorders, medications, chronic renal failure, and ectopic prolactin secretion (see Table 1). The majority of pathological hyperprolactinemia is the result of tumors in the anterior pituitary gland. Prolactinomas account for approximately 40% of all pituitary tumors [26], with a prevalence of 50 per 100 000 [27–29]. Despite their ubiquity, little is known about the cause of of most prolactinomas.

Data from animal studies has been helpful in elucidating the molecular mechanism involved in abnormal lactotroph cell proliferation and secretion. Female prolactin receptor knockout mice have been shown to develop large secreting prolactinomas with 100% penetrance [30▪▪]. Bernard *et al.* attempted to use microarray data to identify genes that are differentially expressed between mice with and without prolactinomas. This research discovered that prolactinomas were associated with a dysregulation in a variety of transcription factors (STAT5, STAT3, AhR, ESR1, BRD4, CEBPD, YAP, FOXO1) and kinases (JAK2, AKT1, BRAF BMPR1A, CDK8, HUNK, ALK, FGFR1, ILK) [30▪▪]. Building further on these findings, another group created a heterotopic allograft model using rat prolactinomas and found that the activins orphan type I receptor ALK7 is expressed on prolactinoma cells, but does not exist in normal prolactin-expressing cells [31▪]. This expression is evolutionarily conserved between rats and humans, and may be a way to distinguish between normally functioning lactotrophs and pathogenic states [31▪].

Translating the findings of animal studies to human studies, there have been conflicting data surrounding whether similar loss-of-function mutations can result in the formation of prolactinomas. Bernard *et al.* [32▪] sequenced the prolactin receptor exons and intron–exon junctions from 88 patients with sporadic prolactinomas, and found that despite identifying four prolactin receptor variants in 16 patients, none had any effect on the prolactin receptor expression, localization, or signaling after prolactin stimulation. Consequently, they concluded that germline mutations in the prolactin receptor were not associated with sporadic prolactinoma. Subsequently, Gorvin *et al.* [33▪▪] identified six different germline mutations in the prolactin receptor, including three rare variants (Glu376Gln, Arg453Trp and Asn492Ile) that were not previously identified in the Bernard *et al.* study, that were found to have a strong association with prolactinomas. The authors of the positive study reconciled the differences of the two studies by citing the different patient populations (older age of onset, more male patients, high number of dopamine agonist-resistant prolactinomas requiring surgery, different ancestry) [33▪▪]. Many questions still remain regarding the mechanisms by which these genetic changes influence disordered prolactin secretion and formation of pituitary tumors.

Although dopamine agonists, such as cabergoline and bromocriptine remain the mainstay of treatment for hyperprolactinemia, approximately 10% of prolactinomas are resistant to this treatment. It is unclear whether these tumors are genetically different from those that are responsive to dopamine agonists, and this remains a promising area for study.

Idiopathic hyperprolactinemia

In the absence of demonstrable pituitary or central nervous system disease and any other cause of prolactin secretion, hyperprolactinemia is considered idiopathic [18]. A subset of these idiopathic cases has recently been attributed to genetic changes. Recently, Newey *et al*. [34] identified a human germline prolactin receptor mutation that resulted in a loss of function of the prolactin receptor and isolated familial idiopathic hyperprolactinemia in three sisters. The heterozygous mutation in the prolactin receptor gene resulted in prolactin insensitivity, but with variable phenotypes. One sister was infertile and the other two were oligomenorrheic. One sister with oligomenorrhea was still able to conceive and gave birth to four children, but subsequently required initiation of a dopamine agonist for the cessation of postpartum galactorrhea.

Another prolactin receptor variant has also been identified that results in paradoxical hyperprolactinemia with the inability to lactate [35▪▪]. A case of a compound heterozygote for loss-of-function variants of the prolactin receptor was recently described. Despite having idiopathic hyperprolactinemia, she was unable to lactate after both of her two deliveries. Neither she nor her parents had issues with infertility.

These prolactin receptor variants provide some insight into how various mutations within the same gene can result in different pathologic phenotypes. It has been suggested that there are other yet-unknown factors that modulate prolactin receptor signaling that may account for the differences observed in the two families.

NOVEL THERAPEUTIC TARGETS

Kisspeptins for the treatment of hyperprolactinemia-induced infertility

New advances in our understanding of the mechanism by which hyperprolactinemia causes hypogonadotropic hypogonadism and infertility have shed light into the possibility of using kisspeptin to reverse some of the reproductive consequences of hyperprolactinemia. A prospective, randomized, double-blinded trial showed that subcutaneous injection of kisspeptin resulted in an acute increase in serum luteinizing hormone and FSH in women with hypothalamic amenorrhea [36]. However, after 2 weeks of twice-daily injections, desensitization occurred, and the luteinizing hormone and FSH responses were significantly lower. In contrast, when patients with hypothalamic amenorrhea were treated with twice-weekly subcutaneous kisspeptin injections, they only experienced partial desensitization, and maintained higher levels of reproductive hormones after 8 weeks compared with control participants [37]. These studies suggest a potential role for kisspeptin use to counteract the suppressive role of hyperprolactinemia on GnRH neurons.

Tyrosine kinase inhibitors

The ErbB pathway has been implicated in lactotroph tumorigenesis and represents a novel therapeutic target for aggressive or dopamine agonist-resistant prolactinomas. Estimated glomerular filtration rate (eGFR) belongs to the ErbB family of membrane receptor kinases. Studies employing transgenic mice models have shown that EGFR overexpression leads to the development of larger tumors [38]. Transgenic mice W/EGFR over expressed had a four-fold to five-fold increase in circulating prolactin levels, which was decreased by 60% after treatment with a tyrosine kinase inhibitor [38]. In preclinical models, tyrosine kinase inhibitor therapy targeting ErbB receptors appears to be efficacious against dopamine agonist-resistant prolactinomas and remains a promising target for additional study.

The ErbB pathway was investigated in human prolactinoma tissue from 29 patients who underwent surgical resection. EGFR expression was positive in 82% of adenomas and ErbB2 was positive in 92% of patients [39]. To test whether inhibition of this pathway could reduce hyperprolactinemia and tumor size in humans, two patients with aggressive, dopamine-resistant prolactinomas were enrolled in a small pilot study were treated with a tyrosine kinase inhibitor (lapatinib) daily for 6 months. The study showed that prolactin levels and tumor volumes were suppressed in both participants treated with tyrosine kinase inhibitors [39]. These results are promising, but larger clinical trials are needed in order to validate this class of drug as a novel therapeutic target for resistant or aggressive prolactinomas.

CONCLUSION

Hyperprolactinemia is a commonly encountered endocrinopathy that has a proven negative effect on fertility. Various causes for hyperprolactinemia have been identified, with prolactinomas being the most clinically relevant entity. As technology improves, superior techniques to distinguish macroprolactinemia from true hyperprolactinemia have emerged, and have decreased the amount of analytical hyperprolactinemia that is observed in clinical practice. Recent genetic studies have brought to light both new explanations for the pathogenesis of prolactinomas, and have described genetic variants that

account for hyperprolactinemia in the absence of a prolactinoma. Understanding how these genetic changes affect transcription of downstream factors may also reveal new therapeutic targets for treatment of hyperprolactinemia and prolactinomas.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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