Review Article

Stress-Induced Hyperprolactinemia: Pathophysiology and Clinical Approach

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While prolactin is most well known for its role in lactation and suppression of reproduction, its physiological functions are quite diverse. There are many etiologies of hyperprolactinemia, including physiologic as well as pathologic causes. Physiologic causes include pregnancy, lactation, sleep-associated, nipple stimulation and sexual orgasm, chest wall stimulation, or trauma. Stress is also an important physiologic cause of hyperprolactinemia, and its clinical significance is still being explored. This review will provide an overview of prolactin physiology, the role of stress in prolactin secretion, as well as the general clinical approach to hyperprolactinemia.

1. Introduction

1.1. Prolactin Physiology

1.1.1. Structure. Prolactin is a peptide containing 198 amino acids; it shares genetic, structural, and binding properties with growth hormone and human placental lactogen [1]. The prolactin gene is encoded on chromosome 6. In circulation, prolactin exists in different forms: a monomeric form whose molecular weight (MW) is 22 kDa, a polymeric form, “big prolactin” whose MW is 50–60 kDa, and a larger polymeric form, “macroprolactin,” whose MW is greater than 100 kDa. The smallest form is biologically active and accounts for 80–95% of prolactin found in circulation. Of note, big prolactin and especially macroprolactin, due to their large size, have increased clearance time however do not contribute to hyperprolactinemia symptoms due to their biologic inactivity [2, 3].

1.1.2. Metabolism. Normal adult serum prolactin levels vary between sexes: for women between 10 and 25 µg/L and 10–20 µg/L in men. Like many hormones, prolactin secretion is pulsatile, with maximum secretion during REM sleep, with typical peak between 4 and 6 AM [1]. Prolactin is eliminated by the liver and the kidney, and the half life of circulating prolactin is 20–50 minutes [1, 2].

1.1.3. Secretion. Lactotrophs, representing about 20% of the cells encompassing the anterior pituitary and found in its lateral portion, secrete prolactin [2]. Control of prolactin secretion is primarily inhibitory, with dopamine suppressing prolactin release, specifically through the pituitary dopamine type 2 (D2) receptors [1]. Prolactin is also synthesized in the decidualized stroma of endometrial tissue; however, this prolactin is unresponsive to dopamine [2]. On the contrary, thyroid-releasing hormone (TRH) elicits prolactin release, with an effect seen within 15–30 minutes of IV infusion [1]. Estrogen mediates this by enhancing the effect of TRH and inhibiting that of dopamine. Vasoactive intestinal peptide, oxytocin, galanin, and PHM-27 induce prolactin release, as does serotonin, which is thought to be the major stimulating factor accounting for the rise of prolactin during REM sleep. Conversely, glucocorticoids, thyroid hormone, GABA, and somatostatin weakly suppress prolactin secretion [1, 4, 5]. Additionally, cytokines IL-1, IL-2, and IL-6 stimulate prolactin secretion, while INFγ and endothelin-3 are inhibitory cytokines [6].
1.1. Function. Along with GH and IL-6 receptors, prolactin receptors are a member of the type I cytokine receptor family. Prolactin is key for induction and maintenance of lactation. It inhibits reproductive function through suppression of GnRH, thus suppressing the release of gonadotropins FSH and LH and impairing gonadal steroidogenesis in women and men [1]. It is important to note that prolactin also plays a role in growth and development, water and electrolyte balance, metabolism, and immunoregulation [7]. Of note, prolactin has been identified to play a vital role in hepatocyte turnover and growth [8], increase intestinal mucosa [9], induce proliferation of vascular smooth muscle [10], as well the B cells of the pancreas [11]. Prolactin stimulates T and B cells, natural killer cells, macrophages, neutrophils, CD34+ hematopoietic cells, and antigen presenting dendritic cells [12]. Additionally, prolactin is produced by adipose tissue and stimulates adipogenesis and inhibits lipolysis; it promotes insulin sensitivity [13].

1.2. Hyperprolactinemia

1.2.1. Epidemiology. Hyperprolactinemia is the most common pituitary hormone hypersecretion syndrome in both men and women [14]; it most commonly affects women aged 25–34 years and male occurrence is 4 times less frequent [15]. Prevalence in the general population is approximately 0.4%, estimated to affect between 10 and 90 people per 100,000 [15, 16]. However, hyperprolactinemia is present in 15–20% of women presenting with menstrual disturbances [2].

1.2.2. Presentation. Clinical presentation of hyperprolactinemia is sex-specific. Women often present with abnormal menstruation, including irregular cycles, amenorrhea, oligomenorrhea, hypomenorrhea, hypermenorrhea, or shortened menstrual cycles (polymenorrhea). Additional findings may include galactorrhea, infertility, decreased libido, dyspareunia, acne, weight gain, increased adiposity, and hirsutism [13–15]. Hyperprolactinemia causes abnormal frequency and amplitude of female LH pulsations, perhaps through interference with positive estrogen effect on midcycle LH release. There is evidence that hyperprolactinemia inhibits gonadotropin release rather than synthesis. Additionally, elevated prolactin directly inhibits basal and gonadotropin-stimulated ovarian secretion of estradiol and progesterone [2]. In women, chronic hyperprolactinemia causes decreased bone mineral density, especially in the setting of significant hypoestrogenism. In men, hyperprolactinemia may present acutely with diminished libido and infertility. Chronic hyperprolactinemia may present with osteopenia, reduced muscle mass, and decreased beard growth [14].

1.2.3. Diagnosis. Clues in patient’s history as well as physical exam may suggest hyperprolactinemia, especially in the setting of evaluation for menstrual disturbances or infertility. Important historical findings include secondary amenorrhea, decreased libido, and galactorrhea. On physical exam, providers should assess mammary glands, skin, in particular looking for presence of acne or hair growth, as well as neurological exam, specifically assessing visual fields. Diagnosis is confirmed with a blood test. Optimal timing of blood test is 2–3 hours after waking. Hyperprolactinemia is diagnosed when blood prolactin concentration is greater than 25 ng/mL. An elevated prolactin level, especially one that is mildly elevated (20–40 ng/mL), should be confirmed with at least two tests to account for circadian fluctuation as well as other environmental factors causing transient elevation; however, it can be diagnosed with a single value if the level exceeds the upper limit of normal by at least five-fold [3, 15]. The hyperprolactinemia rest test, with serial blood sampling from an indwelling catheter as a patient rests in a quiet room, found that samples drawn at 0, 30, and 60 minutes, were sufficient to diagnose stress-induced hyperprolactinemia, with mild to moderate elevations in prolactin, between 20 and 100 ng/mL [17]. Another study found that intravenous catherization with 15-minute rest period did not correct elevated prolactin, which is as expected with the known half life of prolactin [18].

In reproductive age women, it is important to check pregnancy status, as prolactin levels can increase 10-fold in pregnancy, reaching 300 ng/ml in some individuals. Additionally, the macromolecule prolactin, which is not biologically active, has increased clearance time and may contribute to the findings of elevated prolactin levels, without the clinical relevance. If this is suspected, diagnosis of macroprolactinemia can be made by applying polyethylene glycol to patient’s serum before performing the assay, to precipitate the macroprolactin [3]. Etiologies of hyperprolactinemia are listed in Table 1, and pharmacologic agents affecting prolactin levels are discussed in Table 2.

1.3. Prolactin and Stress Response. The physiologic response to stress is complex; it includes norepinephrine release from various parts of the CNS, secretion of epinephrine from the adrenal medulla, as well as hypothalamic-pituitary-adrenal (HPA) axis activation. Stress response also includes the release of prolactin, which is of significant clinical relevance as there is substantial evidence that prolactin plays a significant role in the development of stress-induced pathology, including stress-induced intestinal epithelial barrier dysfunction [25], stress-induced tracheal epithelial barrier dysfunction [26], cardiac dysfunction in peripartum cardiomypathy [27], and psychological stress in the development of cardiovascular pathology [28]. Further understanding the role of prolactin in modulating emotional stress is essential and can provide further insight into systemic conditions arising secondary to hyperprolactinemia.

1.3.1. Stress-Induced Hyperprolactinemia: Physiology. Prolactin receptor expression in the adrenal cortex of several species supports an evolutionary role of prolactin in the stress response [29]. There is a plethora of evidence supporting prolactin’s role in the adrenal gland’s response to stress, including that hyperprolactinemia increases secretion
of ACTH [2, 30, 31], induces adrenal hypertrophy, and increases storage of cholesterol esters [29]. Moreover, it is thought that hyperprolactinemia increases the adrenal cortex’s sensitivity to ACTH, thus resulting in high corticosterone release even in the setting of low levels of ACTH [2]. Prolactin may also directly induce adrenal steroidogenesis; prolactin has been found to increase levels of adrenal androgens, dihydroepiandrosterone and dihydroepiandrosterone sulfate [32], cortisol and aldosterone [33] and stimulate adrenal catecholamine synthesis [7]. Prolactin acts via G-protein adenylate cyclase coupling and cyclic AMP production [34]; it is hypothesized that prolactin-induced corticosterone release is mediated by increased cAMP production [2], as well as via 3β-hydroxysteroid dehydrogenase activity [34]. The role of prolactin in modulating adrenal innervation is controversial [2].

1.3.2. Types of Stress. Considerable prolactin secretion occurs when animals are exposed to physical or psychological stress [37]. In male mice, 15 minute period of restraint stress causes a 7-fold increase in circulating prolactin levels [38]. In these same mice, this stress-induced increase in prolactin was shown to interact with peripheral targets, significantly increasing tyrosine-phosphorylated signal transducer and activator of transcription 5 (pSTAT5) in the arcuate nucleus, median eminence, and zona fasciculata of the adrenal cortex, as well as central targets, reducing pSTAT5 staining of tuberoinfundibular dopaminergic neurons [38]. In mice, prolactin infusion into cerebral ventricles prevented formation of stress-induced gastric ulcers as well as had antidepressant effects during forced swimming [12]. There is evidence that prolactin also mediates pathological effects of chronic stress. Chronic stress induces expression of prolactin receptors in choroid plexus cells [12] and upregulates prolactin receptor expression in the heart [28]. In mice models, stress-derived prolactin generated fibrofatty cells in the heart, which was prevented with administration of prolactin antagonists [28]. This finding suggests a further complexity regarding prolactin’s role in acute vs chronic stress, where acutely it may produce a proinflammatory state, which is protective, but chronic exposure to heads to habituation to prolactin and pathology may ensue.

| Table 1: Common etiologies of hyperprolactinemia [2, 5, 6, 14, 15, 19, 20]. |
|---------------------------------------------------------------|
| Physiologic causes                                              |
| Pregnancy, nipple stimulation, stress, lactation, sexual intercourse/Sexual orgasm, venipuncture, chest wall stimulation (trauma, herpes zoster), high protein diet, exercise, hypoglycemia |
| Pituitary disease                                               |
| Prolactinomas (microadenomas and macroadenomas); acromegaly, empty sella syndrome; lymphocytic hypophysitis |
| Craniopharyngiomas, meningiomas, dysergerniomas, Rathke’s pocket cyst, other tumors, sarcoidosis, eosinophilic granuloma, neuraxis irradiation, arteriovenous malformations, pituitary stalk section |
| Hypothalamic disease                                            |
| Chest wall lesions, spinal cord lesions                         |
| Hypothyroidism, chronic renal failure, hepatic cirrhosis, Cushing’s disease; Addison’s disease, histiocytosis X, temporal arteries inflammation; chronic uremia; SLE; multiple sclerosis; Sjögren’s syndrome |
| Neurogenic                                                     |
| Pseudocyesis, polycystic ovary syndrome; epilepsy; meningitis, mutation in prolactin receptor gene (His188Arg) |
| Systemic disease                                               |
| Hypothyroidism, chronic renal failure, hepatic cirrhosis, Cushing’s disease; Addison’s disease, histiocytosis X, temporal arteries inflammation; chronic uremia; SLE; multiple sclerosis; Sjögren’s syndrome |
| Other                                                          |
| Pregnancy, nipple stimulation, stress, lactation, sexual intercourse/Sexual orgasm, venipuncture, chest wall stimulation (trauma, herpes zoster), high protein diet, exercise, hypoglycemia |
Psychology research has found hyperprolactinemia to be more common in individuals with mental illness than the general population [39]. It is hypothesized that the increase in dopamine in psychosis may be, in part, a regulatory response to down regulate the stress-induced rise in prolactin [40]. Here is evidence that situations associated with passive coping cause an increase in prolactin, however situations of active coping do not affect prolactin [35]. Additionally, childhood exposure to an absent, alcoholic, or violent father may predispose women to developing hyperprolactinemia later in life [41]. Similarly, studies conducted under hypnosis found prolactin secretion increased with anger from humiliating experiences, while cortisol was associated with surprise and intimidation. This finding supports a complex neuroendocrine response to emotional distress that is unjustly simplified and labeled: it is of clinical importance for providers to more pointedly identify stressors and emotions. Psychology research has hypothesized the role of prolactin as a biomarker and regulator of “maternal subroutine,” along with other important hormones, with the goal of optimizing mother-child relationships and as such, has complex relationship with environmental stimuli [42].

1.3.3. Approach. While more research is necessary to guide clinical practice, it is suggested that stress related to seeing the physician can cause elevation in prolactin. It is suggested

| Table 2: Pharmacologic agents affecting prolactin concentrations [21–24]. |
|-----------------------------|-------------------------------------------------------------|
| **Stimulators**             |                                                             |
| Anesthetics, including cocaine |                                             |
| Antipsychotics 1st generation (chlorpromazine***, fluphenazine****, haloperidol***, loxapine***, perphenazine***, pimozide**, thiothixene***, trifluoperazine***) | |
| Antipsychotics, 2nd generation (aripiprazole*, asenapine**, clozapine*, iloperidone*, lurasidone*, olanzapine**, paliperidone****, quetiapine*, risperidone****, ziprasidone***) | |
| Phenothiazines              |                                                             |
| Tricyclic antidepressants (amitriptyline**, desipramine**, clomipramine***, nortriptyline*) | |
| Opiates (methadone, morphine, etc.) |                                                             |
| Chlordiazepoxide            |                                                             |
| Amphetamines                |                                                             |
| Diazepam                    |                                                             |
| Chlorpromazine              |                                                             |
| SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) | |
| Other antidepressants (bupropion, venlafaxine, mirtazapine, nefazodone, trazodone) | |
| **Hormones**                |                                                             |
| Estrogen                    |                                                             |
| Oral-steroid contraceptives |                                                             |
| Thyrotropin-releasing hormone|                                                             |
| **Antihypertensives**       |                                                             |
| α-Methyldopa                |                                                             |
| Reserpine                   |                                                             |
| Verapamil                   |                                                             |
| **Dopamine receptor antagonists** |                                 |
| Metoclopramide              |                                                             |
| **Antiemetics**             |                                                             |
| Sulpiride                   |                                                             |
| Promazine                   |                                                             |
| Perphenazine                |                                                             |
| Metoclopramide****          |                                                             |
| Domperidone (not available in United States)**** | |
| Prochlorperazine*           |                                                             |
| **Others**                  |                                                             |
| Cimetidine                  |                                                             |
| Cyproheptadine              |                                                             |
| Protease inhibitors         |                                                             |
| **Inhibitors**              |                                                             |
| l-Dopa                      |                                                             |
| Dopamine                    |                                                             |
| Bromocriptine               |                                                             |
| Pergolide                   |                                                             |
| Cabergoline                 |                                                             |
| Depot bromocriptine         |                                                             |

Frequency of increase to abnormal prolactin levels with chronic use: ****high >50 percent; ***moderate: 25 to 50 percent; **low <25 percent; *none or low: case reports. Effect may be dose-dependent.
that if the prolactin levels are less than 50 ng/ml, blood sample should be redrawn after the patient has rested in a quiet room for 60 minutes [2, 17].

1.4. Treatment. Approach to treatment requires assessment of severity of symptoms, desire to reproduce, and evaluation of underlying cause. The mainstay for treatment of symptomatic hyperprolactinemia, particularly patient’s with anovulation, infertility, or galactorrhea, is dopamine agonists, specifically bromocriptine and carbergoline. Bromocriptine has a short half life and requires daily (at bedtime) or twice daily dosing and is often associated with gastrointestinal side effects. Carbergoline, a selective D2 receptor agonist, has fewer side effects, greater potency, and longer half life, compared to bromocriptine, and can be dosed biweekly. At high doses (>3 mg daily), however, carbergoline has been associated with hypertrophic valvular heart disease and chronic use at low doses may increase risk of valvular heart disease. If individuals are unable to tolerate oral agents, vaginal agents are available, with fewer side effects. Both bromocriptine and carbergoline are considered safe in early pregnancy and thus can be used in women of reproductive age or those considering conceiving [3].

Alternative treatments are also available, including cyclic progesterin, OCPs, or estrogen replacement therapy [2, 3]. Additionally, there is evidence that adjunctive metformin significantly lowers prolactin levels and alleviates symptoms of hyperprolactinemia as compared to bromocriptine therapy alone [43]. Of note, metformin therapy, when combined with low-dose bromocriptine, was found to improve glucose and lipid homeostasis [44].

1.5. Further Discussion/Future Direction. Prolactin is a unique hormone in its wide reaching effects as well as its modulation by physical, psychological, and environmental factors. While this review provides an overview on the current understanding of the relationship between stress and prolactin, further research is needed to further elucidate the mechanisms of stress-induced prolactin secretion as well as the implications in pathological conditions. In the field of psychiatry, there is increasing interest in the potential role of prolactin as a biological marker of suicidal activity, specifically whether raised postmortem prolactin levels can detect antemortem physical stress [45]. Additionally, further studies are needed to confirm or refute prolactin’s role in the development of psychosis [16]. In regards to hyperprolactinemia in emerging psychosis, women have been found to have higher prolactin levels, even after correcting for biological variation, which may suggest a sex-dependent stress response with prolactin, which should be further elucidated [12]. Moreover, additional research is needed to further elucidate prolactin’s regulatory role in metabolic homeostasis and immune system function.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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