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Review Article

Emerging Research on Prolactin's Non-Classical Roles: Implications for Hypoprolactinemia

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Abstract

Prolactin is well-known for its role in lactation and reproduction, but recent studies suggest it also influences neuroprotection, immune modulation, bone health, and metabolic regulation. Hypoprolactinemia, an endocrine disorder marked by low prolactin levels, is linked to pituitary dysfunction and has implications for metabolic, neurological, and immune systems that remain largely unexplored. This review highlights prolactin's non-classical roles in neurogenesis, cognitive function, mood regulation, immune response, and metabolism, discussing potential links to metabolic disorders, neuropsychiatric conditions, and increased infection risk. It also addresses the diagnostic challenges due to variable prolactin levels and the absence of standardized criteria. Possible therapeutic approaches, including prolactin replacement therapy and lifestyle changes, are considered to alleviate the effects of low prolactin. The review emphasizes the need to recognize hypoprolactinemia as a significant condition with diverse physiological impacts and suggests avenues for future research to enhance understanding and improve patient care.

Keywords: Hypoprolactinemia, Prolactin, Neuroprotection, Immune Modulation, Bone Health, Metabolism.

1. Introduction

Hypoprolactinemia is characterized by abnormally low levels of prolactin in the bloodstream. This condition is quite rare and typically arises alongside other deficiencies in pituitary hormones, often due to disorders such as large pituitary tumors, pituitary apoplexy, or conditions that exert pressure on the sellar region. Isolated cases of hypoprolactinemia are extremely uncommon.

Prolactin is primarily known for its vital role in lactation and reproduction. It is essential for developing mammary glands, prepping the breast for postnatal lactation, producing milk, and sustaining milk flow. In terms of reproduction, prolactin affects the hypothalamic-pituitary-ovarian axis, which plays a significant role in the maturation of ovarian follicles and the process of ovulation.

Recent studies have shed light on some non-traditional functions of prolactin, revealing its involvement in regulating metabolism, including glucose and lipid metabolism. This hormone has been linked to metabolic disorders such as type 2 diabetes, fatty liver, and abnormal lipid levels. Additionally, prolactin contributes to neuroprotection, influences behavior, supports immune function, and helps maintain homeostasis. Low prolactin levels have been associated with an increased risk of metabolic issues, sexual dysfunction, and psychological conditions like anxiety and depression. These insights indicate that prolactin's effects extend far beyond its classic roles in lactation and reproduction, impacting a wide range of physiological systems.

The purpose of this review is to explore the implications of hypoprolactinemia, focusing on the non-traditional roles of prolactin in various physiological systems. By examining how low prolactin levels affect metabolic regulation, neuroprotection, behavior, immune function, and overall homeostasis, this review aims to provide a comprehensive understanding of the potential consequences of hypoprolactinemia beyond its well-known functions in lactation and reproduction.

2. Prolactin's Non-Classical Roles:

- Prolactin and the Brain

Neuroprotection: Prolactin (PRL) has gained recognition for its role in neurogenesis, neuronal survival, and protection against neurodegenerative diseases, expanding beyond its classical functions in lactation and reproduction. PRL exhibits significant neuroprotective effects through various mechanisms.

n terms of neurogenesis, PRL stimulates the proliferation of hippocampal neural precursor cells, thereby enhancing neurogenesis. Research conducted both in vitro and in vivo has demonstrated increased hippocampal precursor cells and improved learning and memory in PRL-deficient mice.[11]

When it comes to neuronal survival, PRL promotes the survival of neurons by activating several signaling pathways. It has been shown to protect hippocampal neurons from oxidative stress by reducing reactive oxygen species (ROS) levels and suppressing pro-apoptotic factors such as BAX and NOX4 via the NF-κB signaling pathway. Additionally, PRL modulates the PI3K/AKT and GSK3β/NF-κB pathways, which contribute to the upregulation of survival genes like Bcl-2 and Nrf2, crucial for neuronal viability under excitotoxic conditions. [12-13]

Furthermore, PRL's neuroprotective effects extend to mitigating excitotoxicity, a common phenomenon observed in neurodegenerative diseases. It reduces intracellular calcium overload and maintains mitochondrial function, thus preventing apoptosis in neurons exposed to glutamate-induced excitotoxicity. Moreover, PRL has been shown to protect against streptozotocin-induced neuronal damage, highlighting its potential therapeutic role in conditions associated with oxidative stress and metabolic disruption.[14-15]

Cognitive Function: Research has shown that prolactin (PRL) plays a crucial role in memory and learning, particularly through its influence on neurogenesis, neuronal survival, and neuroprotection. For instance, Walker et al. found that PRL stimulates the proliferation of neural precursor cells in the hippocampus, which are vital for learning and memory. Mice lacking PRL demonstrated deficits in tasks reliant on the hippocampus, but these deficits were reversed by infusing recombinant PRL directly into this brain region.[11]

In another study, Cabrera-Reyes et al. performed a transcriptomic analysis that revealed PRL treatment in ovariectomized rats led to the activation of genes associated with learning, memory, and synaptic function. This research underscored PRL's role in shaping hippocampal gene networks that are essential for cognitive processes.[16]

Additionally, Moreno-Ruiz et al. discovered that increased serum levels of PRL in female mice enhanced their performance in spatial learning tasks. This improvement was linked to alterations in the dynamics of hippocampal circuits, particularly within the theta frequency band, which is crucial for tasks involving spatial memory.[17]

Torner et al. further demonstrated that PRL helps prevent the reduction of hippocampal neurogenesis caused by chronic stress, promoting the development of neurons that support cognitive functions under stressful conditions.[18]

Together, these studies highlight the significant role of PRL in boosting cognitive functions through its neurogenic and neuroprotective effects within the hippocampus, a key area of the brain involved in learning and memory.

Mood Regulation: Prolactin (PRL) has been found to modulate depression, anxiety, and stress responses through its roles in neurogenesis, neuronal survival, and neuroprotection.

In terms of depression, PRL has been shown to alleviate chronic stress-induced depressive behaviors. Research by Medina et al. demonstrated that PRL treatment in ovariectomized female rats reduced sucrose anhedonia and passive coping behaviors induced by chronic stress, suggesting an antidepressant effect. Additionally, Faron-Górecka et al. found that changes in PRL receptor expression in the brain are linked to stress resilience and the mechanisms of antidepressant action. [19-20]

When it comes to anxiety, PRL exerts anxiolytic effects by modulating the hypothalamic-pituitary-adrenal (HPA) axis and reducing stress-induced anxiety behaviors. Torner et al. provided evidence that intracerebral infusion of PRL in rats decreased anxiety-related behaviors in the elevated plus-maze test, while downregulation of PRL receptors was associated with increased anxiety. This supports the idea of PRL's role in anxiety reduction, further backed by its ability to reduce microglial activation in the hippocampus following chronic stress exposure.[21]

In terms of stress responses, PRL modulates these reactions by attenuating HPA axis reactivity. Torner et al. demonstrated that PRL reduces the stress-induced increase in corticotropin secretion, thereby influencing the neuroendocrine stress response. Furthermore, PRL prevents the chronic stress-induced decrease in hippocampal neurogenesis and promotes neuronal survival, which are crucial for maintaining cognitive and emotional stability under stress.[18][21]

- Prolactin and the Immune System

Prolactin (PRL) plays a crucial role in regulating immune responses, which can subsequently affect memory, learning, depression, anxiety, and stress responses. PRL influences the activities of T-cells, B-cells, and cytokines, leading to various physiological effects.

In T-cells, prolactin (PRL) boosts both proliferation and survival while shaping the T-cell repertoire selection. It fosters Th1 cellular responses and enhances the cytotoxic ability of T lymphocytes. Moreover, PRL influences the expression of T-bet, an essential transcription factor for Th1 responses, via the JAK2/STAT5 pathway. This modulation could affect neuroinflammatory processes, potentially impacting cognitive functions and the regulation of emotions. PRL promotes the proliferation and survival of T-cells, supports Th1 responses, and increases the cytotoxic capacity of T lymphocytes. Additionally, it disrupts the activity of regulatory T cells (Tregs), diminishing their suppressive roles and worsening autoimmune reactions.[22-25]

In B-cells, prolactin decreases the activation threshold of anergic B cells, facilitating their survival and growth. It also boosts the production of autoantibodies by B cells, which is especially significant in autoimmune disorders like systemic lupus erythematosus (SLE). This imbalance may play a role in the neuropsychiatric symptoms seen in autoimmune diseases, including cognitive difficulties and mood disorders. In B-cells, prolactin supports survival and growth by reducing the activation threshold of anergic B cells. This results in heightened autoantibody production, which is characteristic of autoimmune diseases such as SLE. Furthermore, prolactin encourages the differentiation of germinal center B cells into antibody-secreting cells, thereby furthering the creation of pathogenic autoantibodies.[26-27]

Additionally, PRL affects cytokine production by boosting the release of proinflammatory cytokines, including IL-6, IL-12, and IFN-γ, while also regulating anti-inflammatory cytokines like IL-10. This alteration in cytokine levels can influence neuroinflammation and neuroprotection, ultimately impacting cognitive functions such as memory and learning. High concentrations of proinflammatory cytokines are correlated with symptoms of depression and anxiety, whereas anti-inflammatory cytokines may offer protective benefits against neuronal damage caused by stress. Moreover, PRL enhances the production of proinflammatory cytokines, fostering a proinflammatory environment that can lead to the onset and progression of autoimmune disorders. Increased levels of these cytokines have been associated with heightened disease activity in conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[28-29]

- Prolactin and Bone Health:

Prolactin (PRL) plays a crucial role in bone metabolism, influencing both the formation and resorption of bone. Osteoblasts, the cells responsible for bone formation, have PRL receptors, indicating that PRL directly affects these cells. Research conducted on PRL receptor knockout mice has shown that the absence of PRL receptors leads to decreased rates of bone formation and lower bone mineral density (BMD), highlighting the essential role of PRL in maintaining bone mass and supporting healthy bone development.[30]

PRL also impacts bone resorption by regulating osteoclast activity, the cells that break down bone. Elevated levels of PRL, known as hyperprolactinemia, can boost bone turnover by increasing the ratio of receptor activator of nuclear factor kappaB ligand (RANKL) to osteoprotegerin (OPG). This shift enhances osteoclast activity and accelerates bone resorption. The effects of low PRL levels on bone health, however, remain less clearly understood.[31]

- Prolactin and Metabolism:

Prolactin (PRL) improves insulin sensitivity by promoting the proliferation and function of pancreatic β-cells, which are essential for insulin secretion. It also affects hepatic insulin sensitivity through the PRLR/STAT5 signaling pathway. Studies have shown that overexpressing PRLRs in the hypothalamus can enhance hepatic insulin sensitivity in mice. Additionally, PRL enhances glucose uptake in adipose tissue by increasing the expression of glucose transporter type 4 (GLUT4), thereby improving overall insulin sensitivity.[32-34]

PRL also plays a significant role in lipid metabolism by modulating the function of adipose tissue. It encourages adipocyte differentiation and helps reduce adipocyte hypertrophy, which contributes to maintaining healthy adipose tissue. Furthermore, PRL increases the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and adiponectin—two important factors for lipid metabolism and insulin sensitivity. Moreover, PRL decreases the expression of inflammatory cytokines in visceral fat, which helps to alleviate inflammation-related metabolic dysfunction.[33]

3. Clinical Implications of Hypoprolactinemia:

Hypoprolactinemia can significantly impact immune function. This condition may reduce the activity of T-cells and B-cells, which are essential components of the immune system that help combat infections. Consequently, the diminished activity of these cells disrupts the production of cytokines—signaling molecules that regulate immune responses. As a result, individuals with hypoprolactinemia may become more susceptible to infections, as their body's ability to mount an effective defense is compromised.

Reduced levels of prolactin can also have serious repercussions for neurological and psychiatric health. This deficiency may hinder neurogenesis, the process responsible for forming new neurons, which can compromise the survival of existing neural pathways. Such disruptions may exacerbate cognitive impairments, leading to difficulties in memory, attention, and overall mental function. Additionally, individuals with hypoprolactinemia may be more vulnerable to emotional disturbances, increasing the risk of developing conditions such as depression and anxiety, as well as heightening sensitivity to stress.

Furthermore, studies have linked low prolactin (PRL) levels to reduced bone mineral density (BMD) and an increased risk of fractures. For example, patients with prolactinomas, which can cause hyperprolactinemia, often exhibit decreased BMD and a higher risk of fractures. Conversely, low PRL levels impair bone formation and increase susceptibility to osteoporosis and fractures. This correlation is supported by findings that PRL receptor knockout mice display reduced bone formation and lower BMD.[35]

In addition to these effects, low PRL levels are associated with negative metabolic outcomes, including insulin resistance, glucose intolerance, and dyslipidemia. Research has demonstrated that PRL receptor-null mice develop greater insulin resistance and glucose intolerance when subjected to a high-fat diet compared to wild-type mice. In humans, low circulating PRL levels correlate with a higher prevalence of metabolic syndrome, type 2 diabetes, and fatty liver disease. [36]

Moreover, it can negatively impact cardiovascular health by promoting visceral obesity, chronic inflammation, and dyslipidemia, which further elevates the risk of cardiovascular diseases. [38-39]

Hypoprolactinemia is an overlooked endocrine disorder that hasn't received the clinical attention it deserves, along with a clear set of diagnostic guidelines. While prolactin plays a crucial role in various physiological functions—like lactation, reproduction, neuroprotection, and metabolic regulation—most medical focus has been on hyperprolactinemia. This neglect has contributed to the under-recognition and underdiagnosis of hypoprolactinemia.

Diagnosing this condition can be quite tricky due to the subtle and often ambiguous symptoms it presents. Current research indicates that low or undetectable serum prolactin levels, as well as insufficient prolactin peaks during the thyrotropin-releasing hormone (TRH) stimulation test, are key indicators of hypoprolactinemia. However, the absence of agreed-upon cut-off values for both basal prolactin levels and TRH-stimulated responses complicates matters even further.[40]

Moreover, gender differences add another layer of complexity to the diagnostic criteria. Basal prolactin levels and responses to TRH stimulation vary between males and females. Suggested normal ranges propose a minimum of 5 ng/mL for males and 7 ng/mL for females, with peak responses of at least 18 ng/mL and 41 ng/mL, respectively, to TRH stimulation. To establish more precise and widely accepted diagnostic thresholds, further large-scale population studies are needed.[41]

Certain populations are more susceptible to hypoprolactinemia due to various physiological and pharmacological factors. Postpartum women may experience hypoprolactinemia as a result of pituitary damage or Sheehan syndrome, which can lead to impaired lactation and other metabolic dysfunctions. Additionally, individuals taking dopamine agonists, such as cabergoline or bromocriptine, to treat prolactinomas or other pituitary adenomas are at risk. These medications can significantly lower prolactin levels, resulting in hypoprolactinemia and associated metabolic and psychological issues.[41-42]

Individuals with hypoprolactinemia have several treatment options available to them, including prolactin replacement therapy, lifestyle modifications, medication adjustments, management of coexisting health issues, and psychosocial support.

While there isn't currently a commercially available prolactin replacement, research into recombinant human prolactin has shown potential for treating hypoprolactinemia and alactogenesis in women. This experimental therapy has demonstrated promise in significantly boosting milk production, which could aid in lactation.

However, further studies are needed to establish its effectiveness and safety for more widespread clinical use.[1]

Adopting healthy lifestyle habits—such as engaging in regular exercise, following a nutritious diet, and practicing stress management techniques—can help buffer against the metabolic problems associated with low prolactin levels. These problems may include insulin resistance, dyslipidemia, and heightened cardiovascular risk. Also, Patients on dopamine agonists like cabergoline or bromocriptine may need to adjust their doses to prevent iatrogenic hypoprolactinemia. By lowering the dosage, it's possible to restore normal prolactin levels and alleviate symptoms such as sexual dysfunction and depression.

Regular monitoring for metabolic and cardiovascular issues is crucial for those with hypoprolactinemia. Effectively managing these conditions with suitable medical treatments—such as antidiabetic medications, cholesterol-lowering drugs, and antihypertensives—can significantly reduce their overall health impact.

Given the increased risk of depression and anxiety that often accompanies hypoprolactinemia, providing psychological support and counseling is vital. Addressing the psychosocial aspects of this condition can enhance overall quality of life and foster better adherence to treatment plans.

4. Future Research Directions:

To deepen our understanding of prolactin's varied physiological roles and its effects on human health, several key research directions should be explored. This includes mechanistic studies, clinical trials, epidemiological research, and advancements in technology.

Investigating the molecular pathways that link prolactin to its non-classical functions—such as neuroprotection, metabolic regulation, and immune modulation—is essential. Gaining insights into these pathways can illuminate how prolactin affects numerous physiological systems and help uncover potential therapeutic targets. Research should focus on the JAK2/STAT5 signaling pathway, which is a crucial downstream pathway for prolactin receptor signaling, and delve into its implications across various tissues and disease conditions.

With increasing evidence of prolactin's broader physiological functions, it’s vital to conduct clinical trials that assess the efficacy and safety of prolactin-based therapies. These studies should examine the use of recombinant human prolactin in treating metabolic dysfunctions induced by hypoprolactinemia, as well as neuropsychiatric and reproductive disorders. Additionally, the potential benefits of modulating prolactin levels in patients with cardiovascular diseases and autoimmune disorders warrant thorough investigation.

Large-scale epidemiological studies are essential to ascertain the prevalence and effects of hypoprolactinemia in diverse populations. Such studies should aim to establish normative data for prolactin levels across different age groups, sexes, and ethnic backgrounds. Moreover, they should investigate how hypoprolactinemia relates to the risk of developing metabolic syndrome, type 2 diabetes, cardiovascular diseases, and neuropsychiatric conditions.

The integration of artificial intelligence, biomarkers, and wearable technology shows promise for improving the diagnosis and management of hypoprolactinemia. AI algorithms can sift through extensive datasets to pinpoint patterns and predict disease risks, while biomarkers can shed light on prolactin's functions in various physiological contexts. Meanwhile, wearable devices can track prolactin levels and related physiological indicators in real-time, paving the way for early detection and personalized treatment strategies.

5. Conclusion

Prolactin is a hormone primarily known for its role in lactation, yet research has uncovered its involvement in various physiological processes beyond this traditional function. Gaining insights into prolactin's non-classical roles can deepen our understanding of hypoprolactinemia, an often-overlooked endocrine disorder that can significantly affect patient well-being.

Recent findings highlight prolactin's key roles in neuroprotection, immune modulation, and metabolic regulation. In the nervous system, prolactin promotes neurogenesis, supports neuronal survival, and facilitates myelination while also helping to reduce inflammation and oxidative stress. This suggests that prolactin may offer protective benefits against neurodegenerative diseases and mood disorders.

In the context of the immune system, prolactin influences T-cell and B-cell responses, affects cytokine production, and modulates inflammation. These functions could play a critical role in autoimmune conditions and may impact an individual's susceptibility to infections.

Metabolically, prolactin is involved in insulin sensitivity, glucose homeostasis, lipid metabolism, and overall energy balance. Low levels of prolactin have been linked to an increased risk of metabolic syndrome, type 2 diabetes, and cardiovascular diseases.

Understanding the non-classical roles of prolactin is vital for enhancing patient outcomes. The diverse effects associated with hypoprolactinemia underscore the importance of early diagnosis and targeted treatment. Addressing prolactin deficiencies could not only alleviate related symptoms but also reduce the risk of various diseases and improve overall quality of life.

Raising awareness, investing in research, and pursuing therapeutic innovations are crucial in this often-neglected area of endocrinology. Developing prolactin-based therapies, refining diagnostic criteria, and exploring predictive biomarkers can optimize patient care and further our understanding of this complex hormone. Additionally, a table summarizing the classical and non-classical roles of prolactin could be beneficial for a clearer comparison.

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Conflicts of Interest

The author declare no conflicts of interest.

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