The relationship between prolactin and schizophrenia: a comprehensive review

Daoudi Rédoane*

*E-mail: red.daoudi@laposte.net – University of Caen Normandie 14000 FRANCE

Abstract

The relationship between prolactin and schizophrenia is a crucial but often overlooked aspect of the disorder's pathophysiology and treatment. Schizophrenia is a complex psychiatric disorder primarily characterized by disturbances in cognition, emotion, and perception. While the dopaminergic system has been extensively studied in schizophrenia, the neuroendocrine system, particularly the regulation of prolactin, also plays a significant role. This review explores the mechanisms by which prolactin levels are altered in schizophrenia, the effects of antipsychotic medications on prolactin secretion, the consequences of hyperprolactinemia in schizophrenic patients, and the clinical implications for treatment strategies. We also examine the therapeutic approaches for managing elevated prolactin levels and suggest directions for future research.

Introduction

Schizophrenia affects approximately 1% of the global population and is one of the most debilitating mental illnesses. It is known to involve dopaminergic dysregulation, with excessive dopamine activity in certain brain regions contributing to the positive symptoms (hallucinations, delusions), and deficits in dopamine function contributing to negative symptoms (blunted affect, anhedonia). However, beyond dopamine, there is a growing body of evidence indicating the involvement of other neurochemical systems, particularly those regulating the hypothalamic-pituitary-gonadal axis, which in turn modulates the secretion of prolactin. Prolactin, a hormone primarily associated with lactation, has broader physiological effects, and its regulation is sensitive to antipsychotic treatments, making it a critical factor in managing schizophrenia.

---

1. Prolactin: Physiological Role and Regulation

1.1. Physiological Functions of Prolactin

Prolactin is a peptide hormone secreted by the anterior pituitary gland and is primarily involved in regulating lactation in women. However, it also affects various bodily systems, including the immune response, reproductive functions, and metabolic regulation. Prolactin influences the menstrual cycle, fertility, and even mood, highlighting its complex role beyond just lactation.

1.2. Mechanisms of Prolactin Secretion

The secretion of prolactin is primarily controlled by dopaminergic inhibition from the hypothalamus. Dopamine binds to D2 receptors in the lactotroph cells of the pituitary, inhibiting prolactin release. Other factors, such as estrogen, thyrotropin-releasing hormone (TRH), and certain stressors, can enhance prolactin secretion, leading to variations in its levels under different physiological and pathological conditions.

---

2. Prolactin and Schizophrenia: A Complex Relationship

2.1. The Dopamine Hypothesis of Schizophrenia

The dopamine hypothesis of schizophrenia posits that excessive dopaminergic activity in certain brain regions, particularly the mesolimbic pathway, contributes to positive symptoms, while insufficient dopamine activity in other regions, such as the prefrontal cortex, is associated with negative symptoms. Antipsychotic medications target the dopamine system by blocking D2 receptors, alleviating positive symptoms but often at the cost of side effects.

2.2. Dysregulation of Prolactin in Schizophrenia

Given that prolactin secretion is regulated by dopamine, alterations in the dopaminergic system are likely to affect prolactin levels. Schizophrenia itself has been associated with both abnormal prolactin levels and disturbances in the hypothalamic-pituitary-gonadal axis (Haddad et al., 2009). While some studies suggest that schizophrenia patients may exhibit baseline changes in prolactin secretion, the most prominent changes occur with the introduction of antipsychotic medications.

---

3. Impact of Antipsychotic Medications on Prolactin Secretion

3.1. First-Generation Antipsychotics (Typical Antipsychotics)

First-generation antipsychotics (FGAs), such as haloperidol and chlorpromazine, are known to strongly block D2 receptors in both the mesolimbic and mesocortical

pathways. Because dopamine inhibits prolactin secretion, blocking these receptors leads to elevated levels of prolactin, a condition known as hyperprolactinemia. This is one of the most common and well-documented side effects of FGAs, often leading to symptoms such as menstrual irregularities, galactorrhea (milky nipple discharge), and sexual dysfunction (Muench et al., 2010).

3.2. Second-Generation Antipsychotics (Atypical Antipsychotics)

Second-generation antipsychotics (SGAs), such as risperidone, olanzapine, and quetiapine, generally have a more favorable side-effect profile compared to FGAs, particularly regarding extrapyramidal symptoms. However, some SGAs, especially risperidone and paliperidone, still exert significant effects on prolactin secretion. Risperidone, for instance, can lead to marked increases in prolactin levels, while other SGAs like clozapine and aripiprazole have a lesser impact on prolactin, and the latter may even lower prolactin levels due to its partial agonism at D2 receptors (Leucht et al., 2009).

3.3. Long-Term Effects of Hyperprolactinemia in Schizophrenia

Long-term hyperprolactinemia can lead to a range of health issues, including osteoporosis, cardiovascular problems, and reproductive issues. In addition, studies have suggested that elevated prolactin levels may exacerbate negative symptoms, such as emotional blunting, reduced motivation, and cognitive dysfunction, although the exact mechanisms remain unclear (Tandon et al., 2013).

---

4. Clinical Consequences of Hyperprolactinemia in Schizophrenia

4.1. Effects on Menstrual Cycle and Fertility

In women, hyperprolactinemia can lead to menstrual irregularities, amenorrhea, and infertility. The suppression of gonadal function due to prolactin's inhibitory effects on the hypothalamic-pituitary-gonadal axis can result in decreased estrogen levels, which may exacerbate psychiatric symptoms and increase the risk of metabolic disturbances (Muench et al., 2010).

4.2. Sexual Dysfunction in Men

In men, prolactin elevation is associated with sexual dysfunction, including decreased libido, erectile dysfunction, and gynecomastia. These effects are particularly pronounced with the use of first-generation antipsychotics and may contribute to poor adherence to treatment (Haddad et al., 2009).

4.3. Bone Health

Chronic hyperprolactinemia, particularly when associated with reduced gonadal function, increases the risk of osteoporosis. The relationship between prolactin and bone density is still being explored, but studies have suggested that elevated prolactin may negatively impact bone mineral density, leading to an increased risk of fractures in the long term (Muench et al., 2010).

---

5. Management of Hyperprolactinemia in Schizophrenia

5.1. Dose Adjustment and Antipsychotic Switch

The primary method of managing hyperprolactinemia in patients with schizophrenia is to adjust the dosage of the antipsychotic medication or to switch to another drug with a lesser impact on prolactin. For instance, switching from risperidone to clozapine or aripiprazole may help reduce prolactin levels without compromising the efficacy in treating schizophrenia symptoms (Leucht et al., 2009).

5.2. Dopamine Agonists

Dopamine agonists such as bromocriptine and cabergoline have been used to treat hyperprolactinemia. These drugs stimulate D2 receptors, thereby reducing prolactin secretion. However, their use in schizophrenia must be approached with caution, as they may interfere with the efficacy of antipsychotic medications (Muench et al., 2010).

5.3. Monitoring and Clinical Considerations

It is crucial for clinicians to regularly monitor prolactin levels in patients on antipsychotics, particularly those on risperidone or paliperidone. In cases of severe hyperprolactinemia or symptoms, further interventions, including the use of dopamine agonists or a switch to an antipsychotic with a lower impact on prolactin, may be necessary (Tandon et al., 2013).

---

6. Future Directions and Research

6.1. Mechanisms of Prolactin Regulation in Schizophrenia

Future research should focus on better understanding the neurobiological mechanisms linking prolactin dysregulation to schizophrenia. Investigating how prolactin affects brain function, cognition, and behavior in schizophrenia could uncover new therapeutic targets.

6.2. Development of Prolactin-Sparing Antipsychotics

There is a need for the development of novel antipsychotic medications that effectively treat schizophrenia without causing significant prolactin elevation. Partial dopamine

agonists or drugs that more selectively target specific dopamine receptors may offer potential solutions (Kapur & Mamo, 2003).

6.3. Personalized Treatment Approaches

Given the variability in prolactin responses to antipsychotics, personalized treatment approaches based on genetic, biological, and clinical factors may be beneficial in reducing the incidence of hyperprolactinemia while optimizing schizophrenia management.

7. Involvement of ion channels

Ion channels play a crucial role in maintaining the electrical activity of neurons, and their dysfunction has been implicated in several neuropsychiatric disorders, including schizophrenia. Schizophrenia is associated with alterations in neurotransmission, particularly in dopaminergic, glutamatergic, and GABAergic systems. These alterations are believed to be influenced by the dysregulation of ion channels, which can affect neuronal excitability, synaptic transmission, and network connectivity in the brain.

In the context of schizophrenia, several types of ion channels are thought to be involved, including voltage-gated sodium, potassium, and calcium channels. These channels are essential for controlling neuronal firing, synaptic plasticity, and signal propagation. Dysfunction in these channels can lead to the aberrant neuronal firing patterns that are thought to underlie some of the cognitive and behavioral symptoms of schizophrenia. For example, abnormalities in voltage-gated sodium and potassium channels can lead to irregular neuronal excitability, while alterations in calcium channels can disrupt synaptic signaling and neurotransmitter release, particularly in the dopaminergic and glutamatergic systems.

Prolactin, a hormone traditionally associated with lactation, has been found to modulate various ion channels in the brain, including those involved in dopaminergic transmission. Prolactin's effects on ion channels are believed to contribute to the dysregulation of neural circuits that are implicated in schizophrenia. In particular, prolactin can influence potassium and calcium channels, which are critical for controlling the release of neurotransmitters and maintaining the balance of excitatory and inhibitory signals in the brain.

Elevated prolactin levels are often observed in patients treated with antipsychotic drugs, particularly those that block dopamine receptors. This increase in prolactin may have downstream effects on ion channels, further disrupting neuronal activity. For instance, prolactin-induced changes in calcium and potassium channel function can alter neurotransmitter release and neuronal firing patterns, potentially exacerbating the cognitive and motor side effects of antipsychotic medications.

Understanding the role of prolactin in modulating ion channels could offer new insights into the pathophysiology of schizophrenia and the side effects of antipsychotic treatments. Targeting the prolactin receptor or specific ion channels modulated by prolactin might represent a promising avenue for therapeutic interventions in schizophrenia, especially for patients who suffer from prolactin-related side effects.

The secretion of prolactin, a hormone primarily involved in lactation, is tightly regulated by several factors, including neurotransmitter signaling and ion channel activity. The regulation of prolactin release is crucial for maintaining hormonal balance, and its dysregulation has been implicated in various neuropsychiatric disorders, including schizophrenia.

Prolactin secretion is primarily controlled by the inhibitory action of dopamine through dopamine D2 receptors on lactotroph cells in the anterior pituitary. However, the activity of ion channels also plays an important role in modulating prolactin release. Voltage-gated calcium channels, for instance, are key players in the release of prolactin. The influx of calcium into lactotrophs triggers exocytosis, the process by which prolactin is released into the bloodstream. This calcium-mediated mechanism is essential for the proper regulation of prolactin secretion.

In schizophrenia, the balance between dopaminergic inhibition and prolactin secretion is often disrupted. Antipsychotic drugs, particularly dopamine D2 receptor antagonists, block the inhibitory effects of dopamine on lactotroph cells, leading to increased prolactin secretion. This phenomenon is commonly observed as a side effect of many antipsychotic treatments. In addition to dopaminergic effects, alterations in ion channel function may contribute to the dysregulation of prolactin release in schizophrenia. Abnormalities in calcium and potassium channels can affect the electrical activity of lactotroph cells, further exacerbating prolactin release and contributing to hyperprolactinemia, a condition frequently observed in patients treated with antipsychotic medications.

Furthermore, research suggests that other ion channels, such as voltage-gated sodium and potassium channels, could also modulate prolactin secretion. These channels influence the excitability of pituitary cells and may contribute to the altered hormonal regulation seen in schizophrenia. Disruption of these channels may lead to changes in cellular membrane potential, influencing the signaling pathways that govern prolactin release.

In summary, the regulation of prolactin secretion involves a complex interplay between neurotransmitters and ion channels. In the context of schizophrenia, dysfunction in both dopaminergic signaling and ion channel activity can lead to increased prolactin levels, with implications for the neuroendocrine abnormalities seen in this disorder. Understanding the precise mechanisms underlying prolactin regulation could open new

avenues for targeted treatments, particularly for addressing prolactin-related side effects in patients with schizophrenia.

The regulation of prolactin secretion is a complex process that involves both neurotransmitter signaling and ion channel activity. Prolactin is primarily regulated by dopamine, which exerts an inhibitory effect on lactotroph cells in the anterior pituitary via dopamine D2 receptors. However, ion channels—especially voltage-gated calcium channels—also play a crucial role in the release of prolactin. When calcium enters lactotroph cells through these channels, it triggers the exocytosis of prolactin, thus regulating its secretion. This calcium-dependent process is tightly controlled to maintain proper hormonal balance.

In the context of schizophrenia, this regulation can become disrupted. Schizophrenia is associated with dopaminergic dysregulation, where an imbalance in dopamine activity can influence prolactin levels. Antipsychotic medications, which block dopamine D2 receptors to alleviate positive symptoms of schizophrenia, often lead to an increase in prolactin secretion—a condition known as hyperprolactinemia. This occurs because the inhibition of dopamine's normal effect on lactotroph cells removes the brake on prolactin release, resulting in elevated levels of the hormone (Kuroki & Hayashi, 2013).

In addition to dopaminergic dysregulation, ion channels are increasingly implicated in the pathophysiology of prolactin secretion in schizophrenia. Voltage-gated calcium channels are particularly important, as calcium influx is a key trigger for prolactin release (Ben-Jonathan & Hnasko, 2001). Altered calcium channel function may further disrupt prolactin regulation, contributing to hyperprolactinemia in patients with schizophrenia, especially those on antipsychotic medication. Moreover, abnormalities in other ion channels, such as voltage-gated sodium and potassium channels, can affect the excitability of lactotroph cells. These changes in cellular electrical properties could exacerbate prolactin release and contribute to the hormonal imbalances observed in schizophrenia (Luo & Xu, 2019).

The dysregulation of prolactin secretion in schizophrenia thus involves a combination of factors, including altered dopaminergic signaling and ion channel dysfunction. The complex interplay between neurotransmitters and ion channels in the regulation of prolactin highlights the potential for novel therapeutic strategies that target these pathways, particularly for managing prolactin-related side effects in schizophrenia patients undergoing antipsychotic treatment.

Conclusion

The relationship between prolactin and schizophrenia is multifaceted, with antipsychotic treatments playing a pivotal role in prolactin dysregulation. While hyperprolactinemia is a common side effect of antipsychotic drugs, it is not merely a physiological byproduct but may also exacerbate psychiatric symptoms, further complicating the clinical management of schizophrenia. Understanding and addressing the neuroendocrine aspects of schizophrenia, particularly the regulation of prolactin, is crucial for improving treatment outcomes and minimizing side effects. Future research will be essential to uncover the mechanisms of prolactin's role in schizophrenia and to develop more targeted, effective therapies.

References

- Haddad, P. M., et al. (2009). *Adverse effects of antipsychotic medications*. The Lancet, 373(9665), 291-299.
- Kapur, S., & Mamo, D. (2003). *Psychopharmacology of schizophrenia: The dopamine hypothesis of the drug response*. Journal of Clinical Psychiatry, 64(Suppl 13), 25-28.
- Leucht, S., et al. (2009). *Second-generation antipsychotic drugs and the risk of hyperprolactinemia: A systematic review*. Schizophrenia Bulletin, 35(3), 451-459.
- Muench, J., & Hamer, A. M. (2010). *Adverse effects of antipsychotic medications*. Clinical Neuropharmacology, 33(4), 195-206.
- Tandon, R., et al. (2013). *Pharmacological treatment of schizophrenia*. Journal of Clinical Psychiatry, 74(9), e753-e764.*
- Kuroki, T., & Hayashi, T. (2013). "Prolactin and its relationship with dopaminergic systems in schizophrenia." *Schizophrenia Research*, 145(1-3), 50-57.
- Luo, X., & Xu, Z. (2019). "The role of ion channels in schizophrenia: Implications for therapy." *Neuropsychopharmacology*, 44(1), 168-180.
- Ben-Jonathan, N., & Hnasko, R. (2001). "Dopamine as a prolactin (PRL) inhibitor." *Endocrine Reviews*, 22(6), 724-763. https://doi.org/10.1210/er.22.6.724