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Prolactin and Oxytocin in Psychiatry: A Review

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Abstract: Prolactin is a type of polypeptide hormone synthesized and discharged into the stream of blood from the anterior pituitary gland using specialized cells known as lactotrophs. It is a hormone that handles certain processes in females like lactation, breast development process, and several actions to support homeostasis in humans. The monoamines that are important in controlling the secretion of prolactin include dopamine and serotonin. In recent research, few authors have mentioned its use in schizophrenia, affective disorders, premenstrual syndrome, and alcoholism. Oxytocin is a hormone synthesized in the hypothalamus, specifically in the neurons of paraventricular and supraoptic nuclei, known as magnocellular neurons. It is a peptide hormone. It handles a human's social and mental behavior, decision-making skills, interactions with people, and social memories. In recent studies, its role has also been shown in psychiatric disorders like autism, schizophrenia, mood, and anxiety disorders.

Keywords: Prolactin, Oxytocin, Polypeptide hormone, Lactotrophs, Pituitary, Psychiatric disorders

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Introduction

Prolactin is a hormone produced by the anterior pituitary gland that has several roles like lactation, maternal-infant bonding, and many other physiological functions. Dopamine acts as a major precursor in inhibiting the production of prolactin from the hypo-thalamic pituitary circuit in the brain (Rajkumar, 2014). The production of prolactin can be raised by blocking the type-2 dopamine receptors. Prolactin affects the women's brains during the pregnancy period and results in the depletion of hypothalamic-pituitary-adrenal

axis. These conversions in the mother help for a successful reproduction and childbirth (Cochran *et al.*, 2013; Rajkumar, 2014).

Anti-psychotic drugs can cause a raise in the secretion of prolactin. Increased levels of this prolactin can lead to several adverse effects in the body like erectile dysfunction, production of milk in men as well as in women who are not pregnant, infertility problems, amenorrhea, and galactorrhea in women, weight gain, increased chances of cancer, especially breast cancer in women,

schizophrenia, etc. (Torre and Falorni, 2007).

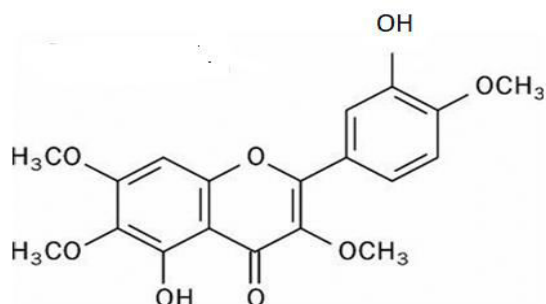


Fig. 1: Chemical structure of prolactin.

Oxytocin (Fig. 2), also known as the love hormone or cuddle chemical, is synthesized in the hypothalamus and acts as a neurotransmitter. Its major functions include stimulation of uterine contractions during labor, influencing libido, parturition, mood, social behavior, and anxiety. In healthy individuals, usually, it causes a decrease in cortisol levels in the body and helps to keep a balance in emotions and moods. It plays a crucial role in stabilizing a person's mood, keeping trust, and recognition, and balancing emotional bonds. In the case of an increase in oxytocin levels, it might cause detrimental emotional oversensitivity. If the oxytocin levels are low, it might cause autism spectrum disorder or depressive symptoms, etc. (Rillema, 1980).

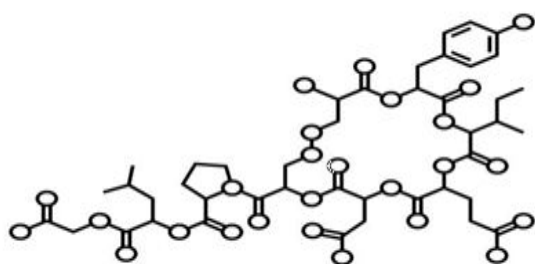


Fig. 2: Chemical structure of oxytocin.

Prolactin dysregulation in psychiatric disorders:

Prolactin is associated with mental illness, psychosis, Major Depression Disorder (MDD), Cardiometabolic Disease (CMD), etc. Higher plasma prolactin levels might lead to symptoms like somatization, anxiety, hostility, paranoid

ideation, and psychoticism. Drugs like Risperidone (Fig. 3), Amisulpride, Clozapine, Olanzapine, Molindone, etc. can cause hyperprolactinemia (Olff *et al.*, 2013). Prolactin levels could be increased due to several reasons like pituitary dysfunctions, hypothyroidism, polycystic ovary syndrome (PCOS), kidney or liver disease, anorexia nervosa, prolactinoma, seizures, lung cancer, stress, or even trauma. The hyperprolactinemic levels of antipsychotics are more sensitive to women when compared to men. A significant role of prolactin includes managing stress and lactation during pregnancy (Shamay-Tsoory and Young, 2016).

Prolactin acts in the dysregulation of psychiatric disorders by reducing the generation of cells within the nervous system in the olfactory bulb, but the inner mechanisms that are undergone are unknown to many. It mostly occurs in the sequence, by the following steps:

1. Decreased intracellular concentration of sodium and increased intracellular concentrations of potassium.
2. Increased levels of cGMP.
3. Reduced level of cAMP.
4. Increased level of prostaglandin synthesis mediated by a stimulation of phospholipase A2 activity.
5. Ultimately leading to a stimulation of polyamine synthesis.

According to few studies it has also been proved that there is a requirement of calcium ions in the extracellular environment for prolactin to show its adverse actions. As it acts in the brain, the prolactin's role in the brain includes acting as a neuropeptide that promotes physiological functions like stress management, reproduction, neuroprotection, etc. Drugs that can be used to treat dysregulation of prolactin in psychiatric disorders include Dopamine agonists, bromocriptine, etc. (Kirsch, 2015). They help in shrinking the prolactinoma and supporting the prolactin levels. They replace the actions of dopamine in the brain. A person using this drug

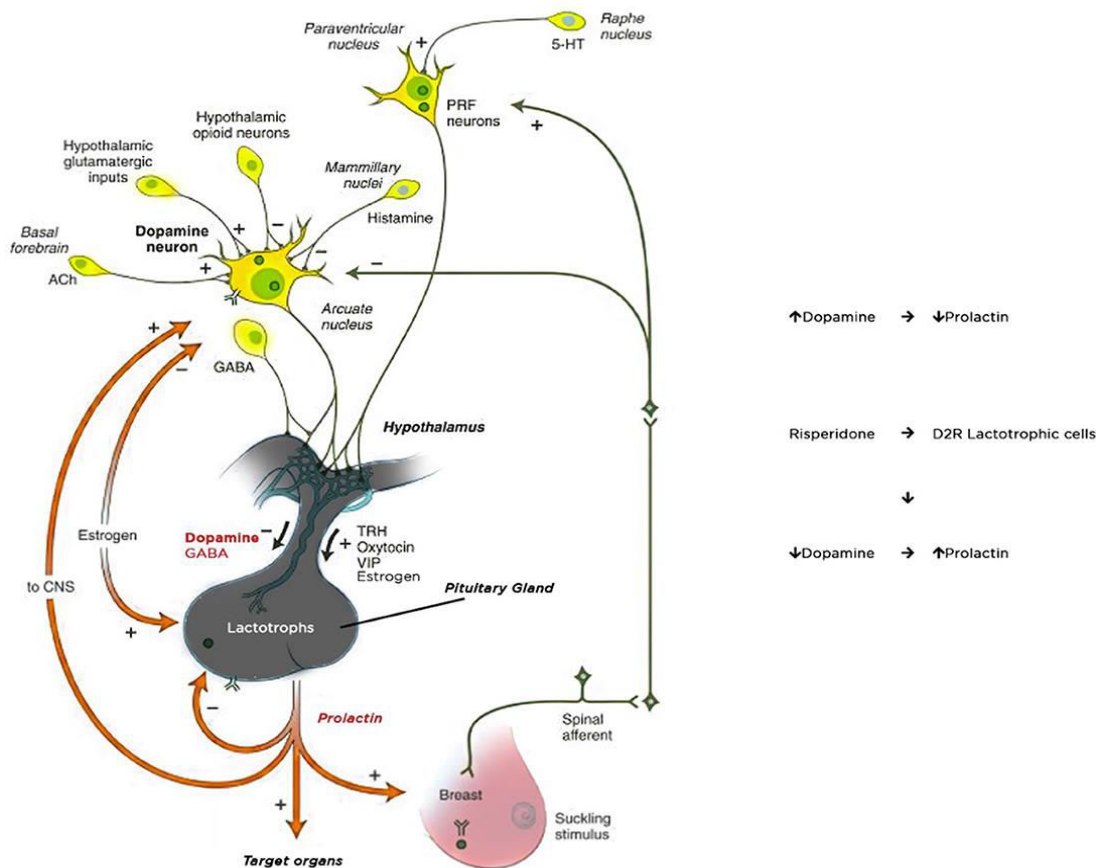


Fig. 3: Risperidone induced hyperprolactinemia.

must use it only under the supervision of a specialized person and continue the medication until there are no traces of prolactinoma (De Cagna *et al.*, 2019). The surgical procedures available to treat and remove prolactin include transsphenoidal surgery and transcranial surgery. In psychosis, increased levels of prolactin due to stress and other reasons trigger release of dopamine by a feedback mechanism. The transmission of dopamine in turn results in the relationship between stress and psychosis (Elgellaie *et al.*, 2021). The study through which it was studied is based on raised levels of prolactin and acute episodes of schizophrenia. It was found that there were several lacunae in that hypothesis; through which there are higher levels of dopamine in tuberoinfundibular pathway due to raised levels of prolactin but, it could not find out if there were any similar changes in the mesolimbic pathway

(Torner, 2016).

Oxytocin and social bonding in psychiatry:

Oxytocin, also known as the love hormone, has a potential link with social bonding and human relations. It influences our behavior, actions, and emotions towards a person or even a situation. Oxytocin hormone helps us sense the difference between good and bad, in case the social environment is “safe” it promotes prosociality, but in case it is predicted to be “unsafe” it releases defensive mechanisms in the body to face the situation (Olf *et al.*, 2013; Shamay-Tsoory and Young, 2016).

Oxytocin has been studied as a potential therapeutic intervention for treating various psychiatric disorders. Oxytocin works by balancing 2 different networks during social behavior. They are amygdale and prefrontal

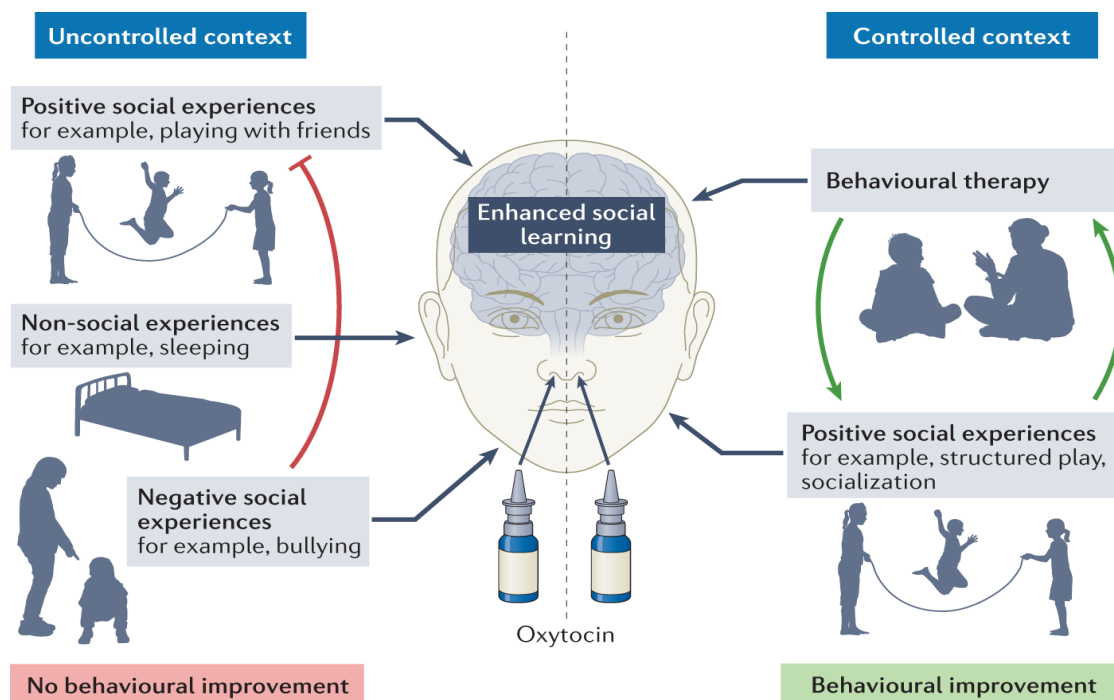


Fig. 4: Oxytocin Therapy for Autism.

networks of the brain. An imbalance/malfunction of this system can result in psychiatric disorders (Donadon *et al.*, 2018). The neuropsychiatric disorders that can be caused by the imbalance of oxytocin include autism, social anxiety disorder, depression schizophrenia, and several other mental disorders. Oxytocin works through activating stimuli and negative feedback mechanisms (Rillema, 1980).

Oxytocin, in recent studies, has been recognized for its actions in increasing social behavior and regulation of stress (Fig. 4). In case the oxytocin levels are increased in the body, it may trigger an imbalance in the detrimental emotional oversensitivity. If oxytocin levels are low, it can result in symptoms like depression and postpartum depression (Alexander, 2012). The medications used for balancing oxytocin levels are Atosiban, Pitocin, Syntocinon, etc., and nasal sprays.

Schizophrenia is a disease associated with disconnection from reality, living in a different world of illusions, and delusions. It is caused due

to the dysregulation of oxytocin and associated pathophysiology. In a study associated with rodents, it was found that there could be both positive and negative symptomatology. There are distinct parts of the brain associated with social cognitive deficits: amygdala, PFC, temporal gyri, and sulci. These findings have resulted in the relationship between oxytocin system and the social brain functions that have given major implications in treatment of schizophrenia (Frijling, 2017).

Oxytocin and anxiety disorders:

Oxytocin plays a leading role in anxiety disorders. Anxiolytic behavior and neurobehavioral mechanisms are affected. Oxytocin affects anxiety by increasing amygdala activity in patients with anxiety, while in others it decreases amygdala activity. Oxytocin has a special ability to subside fear present within us easier (Alexander, 2012). The neurotransmitter, serotonergic and GABAergic systems present within affect both oxytocin secretion and anxiety-related disorders. Low oxytocin levels usually cause social anxiety

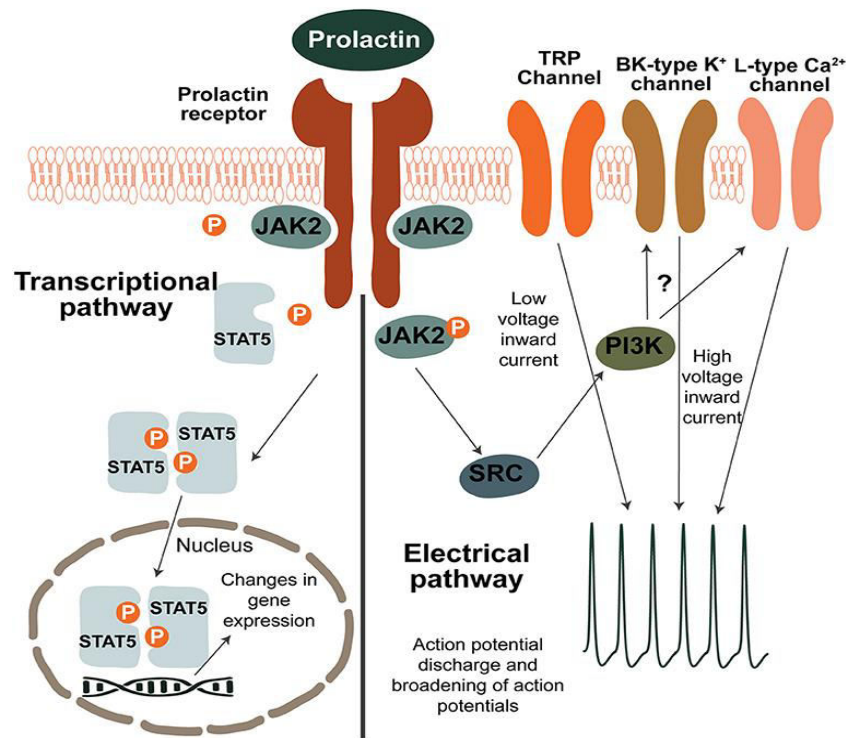


Fig. 5: Prolactin family of hormones as controller of mood and behavior.

disorder, borderline personality disorder, etc. High oxytocin levels can cause several psychiatric disorders like autism, schizophrenia, mood anxiety disorders, prostatic hypertrophy in men, etc. The drug oxytocin controls the triggering of ACC (Anterior Cingulate Cortex) and MPC (Medial Prefrontal Cortex) in patients with social anxiety disorder (Donadon *et al.*, 2018).

The medications used for anxiety disorders include intranasal oxytocin, but it is not yet conclusive with its effects on the disease completely, research is still going on to study and verify its effects. In the first attempt/evaluation, the amygdala hyper-reactivity was reduced after inducing intranasal oxytocin (Mishra *et al.*, 2018). In the second trial, it was noticed that the association between the amygdala, bilateral insula, and cingulate gyrus was improved after administration of intranasal oxytocin in patients suffering with anxiety disorders. In contrast, in others, it did not show any effect. So, the results are not yet confirmed and verified for its activity (Kulkarni, 2018).

Schizophrenia or psychosis usually occurs during late adolescence or early adulthood. In psychosis, a single dose of intranasal oxytocin is used for its treatment, thus enhancing its social functioning and ultimately resting the hippocampal blood flow through it. It then raises the resting cerebral perfusion and ultimately the onset of psychosis (Alexander, 2012).

Prolactin and depression:

Prolactin present in plasma performs functions like regulation of stress, and other similar activities like hostility, anxiety, and weight gain. Plasma prolactin is higher in females when compared with males. As prolactin levels are higher in women, there are studies that say why women cry more than men. It is also known as an adaptive hormone. It is usually present in higher concentrations in patients with mood problems that could lead to depression (Fig. 5) (Kirsch, 2015; De Cagna *et al.*, 2019). Dysregulation of prolactin is one of the major causes of MDD (Major depressive Disorder). Major Depressive Disorder

is associated with deteriorating physical health and increased risks for cardiometabolic diseases, while the link between them and prolactin is still left undiscovered but could be neuroendocrine dysregulation. The results are analyzed by calculating biometric data, BSI (Brief Symptom Inventory), and DASS (Depression Anxiety Stress Scale) (Elgellaie *et al.*, 2021).

The treatment for sadness/depression by higher prolactin levels includes bromocriptine or pergolide. They help in reducing mood disorders and stabilizing a person's mood. The natural remedies to reduce prolactin levels include avoiding gluten, avoiding alcohol, taking Vitamin E and Vitamin B6 supplements, making a balance in blood-sugar levels, avoiding stress, avoiding high-intensity exercises, etc. (Szewczyk *et al.*, 2023).

Oxytocin in PTSD and trauma-related disorders:

In any stressful situation, hypothalamus triggers the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, by releasing hormones like adrenaline and cortisol that help to face a threatful situation. Post-Traumatic Stress Disorder (PTSD) is caused due to decreased levels of Vitamin D in the body. Post-Traumatic Stress Disorder (PTSD) caused by excessive physical or physiological stress. Due to the stress produced the body releases hormones like catecholamines and cortisol as a flight and fight response (Kaiser, 2012). Oxytocin is a hormone that decreases the amygdala reactivity towards the emotional faces in patients with PTSD. In people with recent traumatic experiences, estrogen increases the experience faced by trauma and restores the functions of neuronal networks in the brain associated with fear/anxiety in patients with PTSD (Alexander, 2012).

The common symptoms for PTSD or Trauma include recollecting past or bad experiences, negative thoughts, or emotions, fear, anger, guilt, exaggerated feelings or emotions, rejection, loss of interest in activities, etc. People with PTSD cannot concentrate on the work they are doing, get

irritated easily, get frustrated or engage in wrong and destructive behavior (Alexander, 2012; Frijling, 2017; Donadon *et al.*, 2018).

The treatment for PTSD can be done through methods such as psychotherapy and medications. Medications like antidepressants, anti-anxiety agents, mood stabilizers, alpha-1 blockers, etc. are used for the treatment of PTSD. Selective-Serotonin-Reuptake-Inhibitors (SSRI's) are used as the first line of treatment for patients suffering with PTSD. An example of SSRI's includes Fluoxetine. In antidepressants, the FDA has approved the use of sertraline and paroxetine for the treatment purpose, while the others are still in the stage of research and development. A preventive development measure for PTSD includes inhalation of intranasal oxytocin to stop the development of symptoms of PTSD in earlier stages (Kaiser, 2012).

Hormonal dysregulation and mood disorders:

Hormonal dysregulation occurs mostly in women during menstrual cycles/menstruation and menopause. During menstruation, women have high chances of mood swings and depression. The mood disorders that are associated with hormonal fluctuations include (Szewczyk *et al.*, 2023)-- (i) PMS (Premenstrual Syndrome); (ii) Perimenopausal Depression; and (iii) PMDD (Premenstrual Dysphoric Disorder).

Premenstrual syndrome (PMS):

PMS is a condition in which women have a combination of symptoms both physical and mental. It usually occurs before the beginning of menstruation and after ovulation. The probable reason for this found out by researchers could be a decrease in levels of progesterone and estrogen when the woman does not get pregnant. They become normal once their menstrual cycle begins. It is higher in women above the age of 30 years. In certain women or girls, it is so severe that they might not be able to attend their work or complete their work and at times may have to depend on others (Kaiser, 2012; Mishra *et al.*, 2018).

The common symptoms found for PMS include:

- Mood swings
- Depression
- Appetite change
- Cravings
- Insomnia
- Decrease in concentration levels
- Variations in libido
- Spasms
- Diarrhea
- Tender Breasts
- Fatigue, etc.

The preferred treatment methods for Premenstrual Syndrome include hormonal therapy, use of contraceptive pills, behavioral therapies, antidepressants, and supplements according to dietary needs. It can also be balanced by the intake of vitamin E, vitamin B6, calcium, and magnesium or even by specific exercises and yoga (Kaiser, 2012).

Premenstrual dysphoria disorder (PMDD):

PMDD was earlier known as Late Luteal Dysphoric Disorder (LLDD). It is usually known as an advanced or extreme form of Premenstrual Syndrome (PMS). In PMDD, the symptoms are all the same as PMS but may differ from person to person. As the state is worse when compared to PMS, Women also have a chance of feeling discomfort, high anxiety, depression, and in certain cases may lead to suicidal chances seen in women of any age and even in transgenders who have ovaries. As discussed earlier it could be due to a decline in levels of estrogen and progesterone and the symptoms are reduced once they have their menstrual cycle back as the levels of progesterone and estrogen become normal (Rajkumar, 2014).

Treatment of PMDD includes SSRIs, usage of contraceptive pills, therapies, counseling, anti-

inflammatory drugs, painkillers, GnRH analogue injections, and sometimes even surgery.

Perimenopausal depression:

Perimenopausal depression is a condition before the cessation of menses. Perimenopausal Depression is a state of women that occurs at the age of 40-50 years. In this condition, their mental health is affected badly and causes depression in them. It could be due to this stage known as “perimenopause” i.e. before menopause. At this stage, menses become gradually less frequent (Donadon *et al.*, 2018). It might take a few months to a few years depending on a person’s physical and mental health. In certain cases, it can affect the family, friends, and society also. Its symptoms may include insomnia, social refusal or isolation, stressfulness, tearfulness, etc. Research is still going on for the treatment of perimenopausal depression, but researchers could not yet come to any conclusions or solutions. There is no complete cure for this disease yet, but it can be controlled by the combined treatment of antidepressant and hormone (Bargiota *et al.*, 2023).

Prolactin and oxytocin as therapeutic targets:

Prolactin and oxytocin are both hormones secreted from the hypothalamus and posterior pituitary, respectively. They have noticeable effects in the treatment of migraine. They also have sex- dependent contrasting functions and roles. Oxytocin and prolactin are both part of nociception but acting in contrasting ways at central and peripheral levels. In migraine treatment that targets prolactin, aims at blocking prolactin receptor antagonist or monoclonal antibodies that act at migraine-pain related sites (Bradley and Woolley, 2017; Bargiota *et al.*, 2023). Prolactin actions must be local to keep the body's prolactin levels and avoid adverse effects. In contrast, for Oxytocin targeted treatment, it must improve its signaling and anti-nociceptive activity, for example, inhalation of intranasal oxytocin. For an effective pharmacological treatment of nociceptive receptor, prolactin and oxytocin receptors are co-localized with the estrogen

receptors and calcitonin gene-related peptide and receptor. Oxytocin also has a significant role in male reproductive tract while prolactin has a key role in the female reproductive system as well as during pregnancy and childbirth (Bargiota *et al.*, 2023).

Conclusion

Prolactin a polypeptide hormone that is synthesized in the posterior pituitary has shown significant role in psychiatric disorders, its role in depression and hormonal dysregulation. It has a role in the treatment and regulation of certain diseases, plays a significant role during a woman's pregnancy, and during childbirth. Research can also be performed to improve a woman's health during pregnancy, treat infertility problems, and treat cramps. We can also perform research oriented towards prolactin's specific role in men and women with reproduction and other related sources, also specialized medications used for treatment of imbalance of prolactin levels in human blood and natural methods for supporting prolactin levels. \Oxytocin, also known as love hormone, synthesized by the hypothalamus has been seen as a key part for social bonding and behavior, mood disorders, PTSD, anxiety disorders, and other trauma-related diseases. It has a key role in uterine contractions. Research can be performed on Oxytocin's role in stress relief, medications used for treatment used to balance oxytocin levels in the body.

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