

Prolactin as a factor for increased platelet aggregation

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Abstract

Administration of antipsychotics appears to be related to increased risk of venous thromboembolism and cerebrovascular side effects. The biological mechanism responsible for this possible adverse drug reaction is unknown, but there is a growing number of elucidating hypotheses. Treatment with antipsychotics is associated with elevation of prolactin level.

Prolactin has recently been recognized as potent platelet aggregation co-activator, and have therefore been postulated as an additional risk factor for both arterial and venous thrombosis. We briefly review the arguments for the role of hyperprolactinemia in pathogenesis of platelet aggregation.

PSYCHOTROPIC DRUGS AND PROLACTIN LEVELS

Prolactin is a polypeptide hormone secreted by the lactotroph cells of the anterior pituitary gland. The most common role of prolactin is the induction and maintenance of lactation. Additionally, it interferes with regulation of other CNS (central nervous system) and peripheral processes (maintenance of mineral and water balance, growth and development, endocrine and metabolic processes, and immune system). Prolactin influences reproduction, fertility and sexual behavior in humans.

Prolactin secretion is regulated by both direct and indirect influence of a wide range of stimulatory and inhibitory substances. The main prolactin-inhibiting factor is dopamine. Dopamine secreted in the tuberoinfundibular tract inhibits prolactin release via its action on D2 receptors located on the surface of lactotroph cells. Serotonin stimulates prolactin secretion. This action is probably mediated by thyrotropin-releasing hormone, vasoactive intestinal polypeptide and peptide histidine methionine. Prolactin is also released in response to nipple stimulation during breastfeeding or in response to stress. Endogenous substances such

Table 1. Clinical adverse effects associated with hyperprolactinemia (adapted from Halbreich et al., 2003).

| |
|---|
| Galactorrhea |
| Increased risk of breast cancer |
| Osteoporosis |
| Infertility |
| Decreased testosterone levels and sperm mobility |
| Sexual dysfunction |
| Disturbed menstrual cycles, anovulation, amenorrhea |

as estrogens, opioids or substance P increase prolactin secretion while GABA (gamma amino butyric acid) and acetylcholine work as prolactin secretion inhibitors [8]. Figure 1 shows the relevant regulatory mechanisms of prolactin secretion.

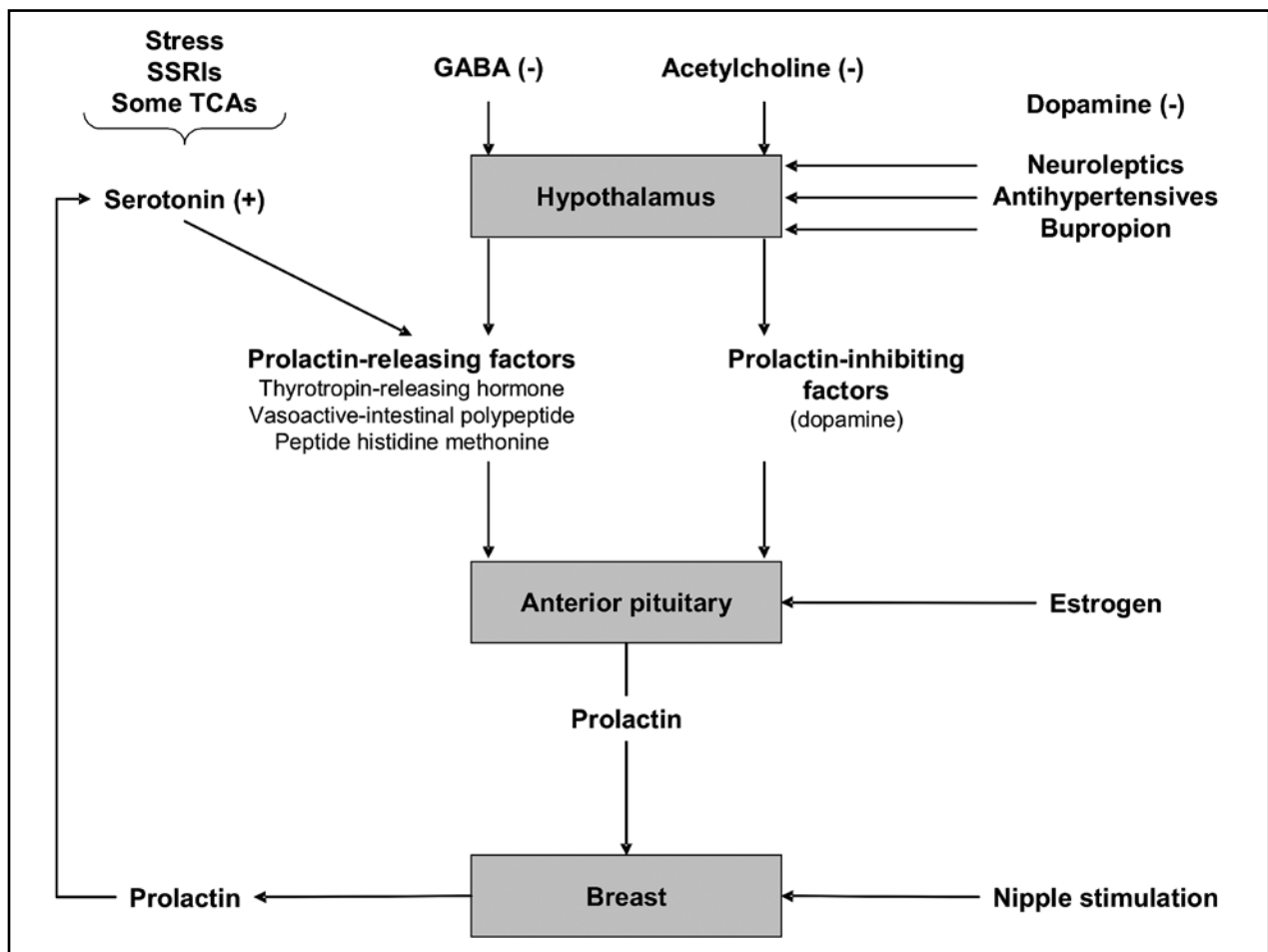
Elevated prolactin level may directly or indirectly lead to a wide range of pathological states. Table 1 presents the possible clinical conditions associated with hyperprolactinemia.

The affection of prolactin level is recognized as one of the adverse effects of antipsychotic treatment and as such may be associated with similar clinical consequences.

Elevation of prolactin level is predominantly associated with conventional neuroleptics but may develop also during the treatment with second generation antipsychotics. For example, risperidone induces hyperprolactinemia to a similar level to that of the conventional agents. Even low doses of risperidone used as an augmentation to antidepressants are associated with hyperprolactinemia and can induce endocrinological side effects [17]. There is evidence that amisulpride, even in low doses, and zotepine cause the elevation of prolactin level [14,18,32]. Additionally, hyperprolactinemia associated with the treatment with ziprasidone has been reported [19]. Treatment with antidepressants can also be associated with hyperprolactinemia [11].

One of the less known adverse effects of antipsychotic treatment is increased risk of venous thromboembolism [26,35]. Recently a higher incidence of cerebrovascular complications has been reported [33,34]. The results, however, were questioned by some authors who interpreted the outcomes as an artifact due to selection bias [12,24].

There is evidence that patients with hyperprolactinemia have increased risk of thromboembolic complications. Though the precise mechanism has not yet been fully clarified, it seems that elevated prolactin level may play an important role in the pathogenesis of venous thrombosis.

**Figure 1.** Regulatory mechanisms of prolactin secretion (adapted from Halbreich et al., 2003).

PROLACTIN AS A COFACTOR FOR PLATELET ACTIVATION

Platelets play a crucial role in arterial and venous thrombosis. They participate in hemostatic processes via mediation of a wide range of interactions between the blood and vessel endothelium in so called primary hemostasis. Primary hemostasis is a process of primary hemostatic clot formation in response to bleeding and is mediated mainly by the interaction between the platelet and vessel wall. Circulating platelets are very labile and respond to changes of the environment. The most commonly recognized reactions of platelets are the adhesion, shape change and aggregation. Adhesion is the attachment of platelets to any surface other than surface of another platelet. Aggregation is the accumulation and connection of platelets in order to create thrombus. During the activation the platelets loose their discoid shape and start to develop pseudopodia. The presence of von Willebrand factor is essential for adhesion of platelets. It provides the connection of the appropriate receptor on vessel endothelium with glycoprotein I on platelets. Aggregation of platelets is mediated by a complex mechanism dependent on Ca^{2+} , glycoprotein IIb/IIIa and fibrinogen. The primary aggregation agent is adenosindiphosphate.

Thromboxane A_2 , collagen and the platelet and platelets lipids activating factor are the other inducers of aggregation. Adhesive molecules and serotonin also play a role in this process. The last step of primary hemostasis is represented by retraction of the created blood clot mostly by the contribution of glycoprotein IIb/IIIa [23].

It has been suggested that platelet activation is an important initial step of the process of hemostasis and therefore increased activation of platelets in circulation can contribute to the pathogenesis of thromboembolic complications and atherosclerosis [28]. There is an evidence that prolactin could be one of the platelet co-activators [28,29,30,31].

The hypothesis concerning the prolactin participation in development of venous thromboembolism is based on observations of increased incidence of thromboembolic complications in pregnancy and during lactation. About 50% of such cases may be explained by exogenous factors such as immobilization, obesity, trauma, operation or congenital coagulopathies. In many cases there is a comorbidity of congenital and acquired factors. However, a portion of venous thromboembolic complications is still referred to as idiopathic.

Wallaschowski and colleagues hypothesized that increased prolactin level is a contributing factor in platelet

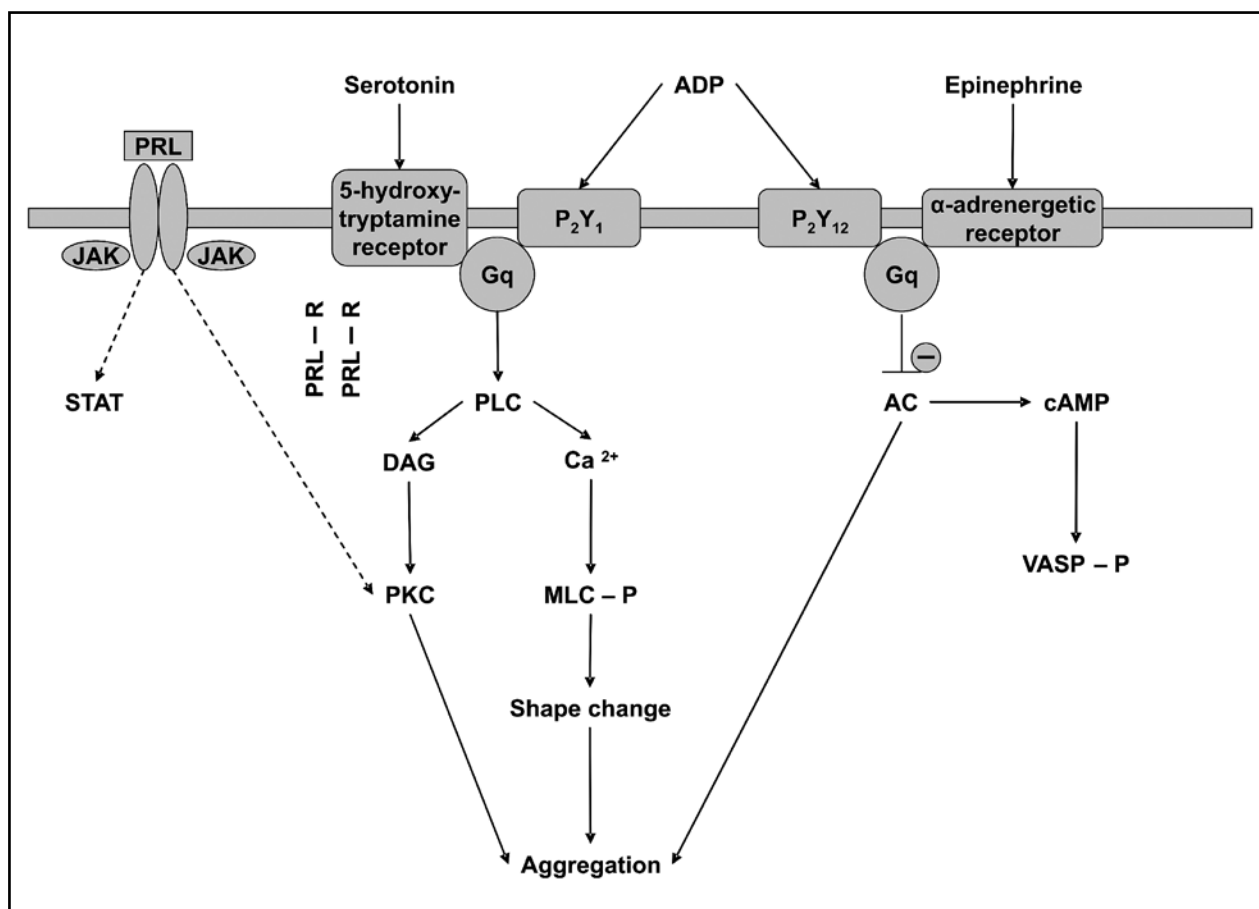


Figure 2. The mechanism of prolactin involvement in the process of platelet aggregation (adapted from Wallaschowski et al., 2003). DAG: 1,2-diaclyglycerol; JAK: janus kinases; MLC: myosin light chain; PLC: phospholipase C, STAT: signal transducer and activator of transcription; VASP: vasodilator-stimulated phosphoprotein.

activation process. This hypothesis has been based on their clinical observations of pregnant women, patients with pituitary tumors (normo- or hyperprolactinemic) and healthy controls. In addition, they studied the *in vitro* platelet activation and aggregation in healthy controls' blood samples. According to the results of their investigation, Wallaschofski and colleagues concluded that prolactin may be a physiological co-factor in process of coagulation in pregnancy and may explain increased risk for thromboembolic complications around delivery. In another study a significantly higher stimulation of platelets was found in patients with hyperprolactinemia caused by antipsychotic treatment when compared with normoprolactinemic controls [29].

The mechanism of prolactin involvement in the process of platelet aggregation was described by Wallaschofski and is shown in Figure 2. High doses of prolactin enhance the ADP-stimulated aggregation of platelets. Apparently, prolactin *per se* does not influence the process of aggregation, for it does not enhance the aggregation stimulated by thrombin or collagen. Alpha 2 receptor activation is transduced by Gi protein (coupled to ADP P2Y12 receptor), since serotonin is associated with Gq protein activation (coupled to ADP P2Y1 receptor). Prolactin and adrenalin separately do not lead to platelet aggregation but their combination does. Serotonin itself leads to a weak platelet aggregation and the effect is not stronger when combined with prolactin. The combination of serotonin and adrenalin leads to full-blown platelet aggregation indicating that prolactin is associated with Gq protein. Gq protein induces the shape change of activated platelets. However, only serotonin but not prolactin induces a shape change of platelets. This means that prolactin receptors are not directly connected to Gq proteins but bypass G-protein-related pathways and may directly interact with protein kinase C. Protein kinase C is one of the key enzymes in signal transduction pathway coupled with protein Gq. Prolactin receptors are not of kinase origin, therefore receptor binding kinases (so called "janus kinases") are necessary for their activation. Prolactin also contributes to platelet activation via an additive effect in protein kinase C phosphorylation [30].

OTHER COFACTORS OF THROMBOEMBOLIC COMPLICATIONS ASSOCIATED WITH ANTIPSYCHOTIC TREATMENT

Phenothiazines [6,7] and clozapine [10,16] were the first antipsychotics associated with increased risk of venous thromboembolism. A high incidence of thromboembolic complications has also been reported in association with risperidone and olanzapine [9].

In recent years, there has been a significant progress in research concerning etiology of venous thromboembolism, especially the role of coagulopathy [25].

The multifactor nature of venous thromboembolism is undisputed. The hypothesis concerning the influence

of antipsychotic treatment has to be seen in the context of three basic factors involved in pathophysiology of thromboembolism [22]. **A damage to vessel wall** does not apply in the case of antipsychotic treatment, but **venous stasis** does. Antipsychotic drugs often used in combination with benzodiazepines cause sedation with reduced activity contributing to venous stasis. The lifestyle of the patients under long-term antipsychotic treatment is characterized by lack of exercise, unhealthy diet and weight gain. Specific example of reduced activity is physical restraint. The third important factor in the pathophysiology of thromboembolism is **abnormal process of coagulation**. Drugs as phenothiazines [15] and clozapine [4, 10] are associated with increased level of antiphospholipid antibodies with pro-thrombogenic properties. We observed a case of antiphospholipid syndrome with positive lupus anticoagulans antibodies probably induced by clozapine treatment. The patient experienced accompanying spontaneous massive pulmonary embolization [21]. Canoso and Oliveira [3] reported increased level of antiphospholipid antibodies in a cohort of patients treated with chlorpromazine but they did not find a higher incidence of thrombosis among their patients.

Serotonin-induced increased aggregation of platelets during the treatment with phenothiazines was reported by some authors [1]. High affinity of clozapine and risperidone to 5-HT_{2A} receptors may be responsible for 5-HT_{2A}-induced increased platelet aggregation [15]. In addition to the influence of antiphospholipid antibodies and serotonin on blood coagulation, hyperprolactinemia was investigated (see above).

Hindersin and colleagues described a high coagulation activity associated with increased adrenalin release in an acute psychotic state [13].

CLINICAL IMPLICATIONS

It appears that more and more factors possibly contributing to increased risk of venous thromboembolism are discovered. Based on the current knowledge, a theoretical model of their possible negative interactions with blood coagulation process can be made. Phenothiazines in addition to their massive sedating effect also block 5-HT₂ receptors, cause hyperprolactinemia, and may induce the increase of antiphospholipid antibodies level. They are the group of antipsychotics with the highest risk for venous thromboembolism. Risperidone increases the risk mainly through blockage of 5-HT_{2A} receptors and induction of hyperprolactinemia. The influence of lifestyle and other clinical and laboratory risk factors cannot be left apart. Other factors considered in association with venous thromboembolism are so called "protective mechanisms" – for example obese patients have decreased fibrinolysis due to decreased functioning of plasminogen tissue activator [2].

Additionally, it has to be considered that the evidence so far is based mainly on single observations or *in vitro* experiments.

Hyperprolactinemia does not have to be associated with clinical signs and symptoms. One of the explanations is, that except from prolactin monomer, there are also fragments and polymers of different sizes with variable physiological actions. Therefore, detected prolactin polymers may not be physiologically active [14].

We present a short case of a patient with thromboembolic complication in which hyperprolactinemia was one of possible risk factors.

CASE REPORT

A forty years old obese (body mass index = 40) Caucasian woman with a history of pituitary microadenoma (prolactinoma) and associated hyperprolactinemia was admitted to the hospital due to pulmonary embolism verified by perfusion scan. Chest X-ray findings were normal. ECG recording indicated right ventricular overload. The size of the right ventricle was borderline according to heart echography and no clinical signs of pulmonary hypertension were present. Thrombosis of distal part of the peroneal vein in the right patient's leg was detected by Doppler ultrasound. Gynaecological examination and abdominal ultrasonography revealed no malignity. A comprehensive laboratory testing was performed (blood count+differential, INR, APTT, glucose level, fasting lipid profile, liver tests, creatinin, urea, bilirubin, Na, K, Cl, Ca, TSH). All results were within normal range except from mild elevation of ALT and AST levels (0.70 and 0.70 ukat/l, respectively). Antithrombin level (117%) was normal. In comparison to prolactin level (1911 mU/l; normal values: 50–360 mU/l), other hormonal profile was normal (estrogen, FSH, LH). Complete thrombophilia screening was done (factor V Leiden mutation, factor II 20210 G/A mutation, antithrombin, protein C, protein S, activated protein C resistance, factor VIII, anticardiolipine antibodies and lupus anticoagulant were in normal range).

The patient was treated with low-molecular-weight heparin enoxaparin at doses of 1.0 ml s.c. twice a day. Enoxaparin has been administered for twelve days and then switched to warfarin. The patient was discharged from the hospital in a stable condition shortly after warfarin treatment had been introduced.

Of the common venous thromboembolism risk factors, obesity and hyperprolactinemia were present in this case. However, the patient was also admitted to the hospital due to gastroenterocolitis three weeks prior to pulmonary embolism. Apparently, that event could have contributed to deep vein thrombosis because it was associated with dehydration and a four-day immobilization of the patient.

CONCLUSION

The risk of pathological coagulation associated with the antipsychotic treatment is relatively low; however, it may have fatal consequences (pulmonary emboliza-

tion). Prolactin is just one of the possible risk factors of thromboembolism. A possibility to prove prolactin prothrombogenic properties would be a good reason for prolactin levels monitoring in patients treated with antipsychotics. Knowledge of all the potential risk factors should be applied when choosing the most suitable pharmacotherapy for each patient.

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