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Platelets: A possible glance into brain biological processes in schizophrenia

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Abstract

Schizophrenia is a severe mental disorder, characterized by behavioral, emotional and cognitive disturbances, which commonly follows a chronic course. Diagnostic accuracy, management plans, treatment evaluation and prognosis are dependent on relatively subjective assessments. Despite extensive research and improvement in imaging technology, as well as modern genetic and molecular methodologies, the biological basis of this disease is still unclear. Therefore, there is a need for objective and valid biological markers. Platelets have often been used as a model in neurobiological research. The accessibility of platelets and their similarities with neurons turns them into an attractive candidate to search for biological markers for diagnosis and for unraveling pathophysiological processes relevant to the etiology of brain disorders, including schizophrenia. The present review addresses the main changes in platelet physiology observed in schizophrenia and its response to antipsychotic medication. We summarize numerous studies demonstrating impaired metabolism, uptake and receptor kinetics of schizophrenia-relevant

neurotransmitters, abnormalities in membrane derived phospholipids and polyunsaturated fatty acids, as well as dysfunctions in the mitochondria. These changes fit with the various hypotheses raised for the etiology of schizophrenia, including the dopamine-glutamate hypothesis, the autoimmune hypothesis, the polyunsaturated fatty acid hypothesis and the impaired energy metabolism hypothesis. Despite extensive research in platelets, no conclusive reliable biomarker has been identified yet. This review suggests that the clinical heterogeneity and the biological complexity of schizophrenia lead to the inevitable conclusion that biomarkers will be identified only for subgroups characterized according to the different diagnostic criteria. Moreover, any biomarker would have to be an array of interrelated factors or even a set of several such arrays.

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Key words: Platelets; Schizophrenia; Biomarkers

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INTRODUCTION

Schizophrenia is a devastating psychiatric disorder with diverse clinical manifestations. Life-time prevalence of this disorder is approximately 1% and it commonly follows a chronic course with an onset at late adolescence. Schizophrenia is characterized by cognitive, emotional

and behavioral abnormalities^[1-3]. These psychological and behavioral characteristics are associated with a variety of impairments in occupational and social functioning. The characteristic symptoms of the disease are often conceptualized as falling into two broad categories, positive symptoms and negative (or deficit) symptoms, with a third category, disorganized, recently added. The positive symptoms include delusions and hallucinations. Negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia and decreased initiation of goal-directed behavior (avolition)^[4]. Disorganized symptoms include disorganized speech^[5], disorganized behavior and poor attention. No single symptom is pathognomonic of schizophrenia. The disorder is noted for its great heterogeneity across individuals and for its variability within individuals over time, with alternations between psychotic episodes and residual states^[6-8]. Diagnostic accuracy, prognostication, management plans and treatment evaluation are dependent on relatively subjective assessments. Therefore, there is a need for objective and valid biological markers. This need was raised at least six decades ago when the first antipsychotic drug was introduced, what we call the biological era in psychiatry. Despite extensive research and improvement in imaging technology, as well as modern genetic and molecular methodologies, the biological basis of this disease is still unclear. The heterogeneity of patient population, the diverse characteristics of schizophrenia itself, as well as confusion in diagnostic criteria, adds obstacles in the endeavor to reach this goal. In addition, the long-term therapy of schizophrenia frequently causes numerous effects which further complicate laboratory research.

The last decades have seen rapid progress in the development of noninvasive technologies to study human brain structure and function, yet there remain substantial limitations in our ability to investigate the human brain. Therefore, many experimental attempts have been made to generate reliable blood-derived candidate biomarkers based on the current models of disease pathogenesis. Platelets have often been used as a model in neurobiological research. Platelets and neurons do not share a common embryological origin as the platelets are formed from megakaryocytes that originate from the mesoderm and the neurons are formed from the ectoderm. Regardless of their embryonic origin, platelets and neurons demonstrate similar pathologies in many neuropsychiatric diseases, including Alzheimer's and Parkinson's diseases, schizophrenia and major depression. Platelets, like brain cells, are part of the amine precursor uptake and decarboxylation system described by Pearse^[9]. Other similarities that rationalize the use of platelets as a model for neuronal biochemistry include: active transport system for serotonin (5-HT)^[10], binding sites for many drugs and neurotransmitters, dense bodies which store 5-HT, and mitochondria expressing monoamine oxidase-B (MAO-B). In addition, drugs that affect the metabolism and release of CNS amines, including dopamine, 5-HT

and norepinephrine, also release amines from platelets^[11]. The interest in platelets as a tool for schizophrenia research arose a few years after the isolation of serotonin from the serum in 1948^[12] and the observation of Gaddum *et al.*^[13] that the peripheral effects of serotonin could be antagonized by the known psychotomimetic drug Lysergic acid diethylamide (LSD). By the end of the 50s, the first studies of platelet serotonin concentration in schizophrenic patients had been published, demonstrating high levels of platelet 5HT in psychosis^[14,15]. The second important step was the report by Murphy *et al.*^[16] in 1972 on lower platelet MAO activity in patients with schizophrenia compared to healthy subjects, which opened an era of MAO activity research in psychiatry. Numerous studies have shown that platelets from schizophrenic patients behave differently than those isolated from healthy controls in dopamine uptake, 5-HT content arachidonic acid metabolism, inositol phosphate levels and disturbance of calcium homeostasis^[17-19]. The accessibility of platelets and their similarities with neurons turn them into an attractive candidate to search for biological markers for diagnosis and for unraveling pathophysiological processes relevant to the etiology of schizophrenia. Numerous studies have used platelets in attempt to identify a biomarker for various neuropsychiatric disorders, including Alzheimer's and Parkinson's disease, as well as major depression. This article will focus on the main findings in platelets in schizophrenia. These studies in platelets have been undertaken in an attempt to develop a biomarker for this heterogeneous disorder. While the data in platelet research did not pinpoint a clear single biomarker, there is mounting evidence of multiple impaired factors. Combining these factors into a single array may produce a profile that converge multiple biological abnormalities that will contribute to the diagnosis and to novel treatment strategies in schizophrenia.

SCHIZOPHRENIA RELEVANT NEUROTRANSMITTER SYSTEMS

MAO activity

Monoamine oxidase (MAO) is a mitochondrial bound enzyme, which catalyzes the oxidative deamination of a variety of monoamines, including dopamine, 5-HT and noradrenaline. MAO exists in two catalytically active forms, MAO-A and MAO-B, encoded by separate genes located on chromosome X^[20]. In brain, the ratio of the two enzymes is in favor of MAO-B, while platelets contain only the MAO-B form^[21].

Two decades after the initial report by Murphy and Wyatt in 1972 on lower platelet MAO activity in patients with schizophrenia compared to healthy subjects^[16], numerous studies were performed to replicate their findings or refine them to specific sub-groups of schizophrenia patients.

MAO activity shows gender differences and is lower in men than in women^[22]. During the life span, it tends to increase with age^[23] and in women, MAO activity is

Table 1 Variations in monoamine oxidase activity in health and disease

High platelets MAO activity	Low platelets MAO activity
Women	Men
Elderly	Premenstrual phase in woman
Anxiety states	Bipolar disorder
Alzheimer disease	Alcoholism
	Schizophrenia

MAO: Monoamine oxidase.

decreased during the premenstrual phase^[24], in pregnancy and post-partum^[25]. In the general population, reduced platelet MAO activity was found to correlate with neurotic personality, psychiatric morbidity^[26] and suicidal behavior^[27]. In patients with psychiatric disorders, MAO activity was found to be reduced in bipolar depression compared to unipolar depression^[28], higher in anxiety states^[29] and Alzheimer's disease^[30], and lower in alcoholism^[31] and schizophrenia (Table 1).

In schizophrenia, genetic studies in monozygotic and dizygotic twins indicated a genetic control^[32]. For example, platelet MAO activity, determined in 102 patients with chronic schizophrenia, 223 first-degree relatives and 88 normal control subjects, was shown to be a heritable and stable trait and was significantly lower in patients than in normal control subjects^[33]. Using the transmission probability model, the familial transmission of MAO activity was consistent with either recessive or additive inheritance, but not with dominant inheritance^[34]. Between schizophrenic patients, significantly lower MAO activity was found in chronic patients with a family history of schizophrenia compared to schizophrenics with no affected relatives and to normal controls^[35]. Within families, MAO activity distinguished ill from well relatives. However, the considerable overlap in enzyme activity between affected and unaffected individuals limited the usefulness of low MAO activity as a major risk factor or a biomarker in schizophrenia^[35]. In contrast, other studies did not find a significant difference between drug-free schizophrenic patients with or without a family history of the illness and healthy normal controls^[36]. In addition, a study in children with schizophrenia found no significant correlation in MAO activity between patients and their parents^[37].

In order to establish a clinical relevance for platelet MAO activity, the effect of antipsychotic drugs was also studied. In a meta-analysis study of fifty studies which were published through the 70s and 80s on platelet MAO in schizophrenia, it was shown that, in most studies, antipsychotic medicated schizophrenia patients had lower platelet MAO activity than healthy controls^[38]. Indeed, administration of antipsychotic drugs was shown to lower MAO activity. For example, in platelets derived from patients after 14 and 21 d of haloperidol treatment, MAO activity was significantly reduced, yet did not correlate with the response to treatment. *In vitro* studies confirmed the ability of haloperidol to decrease MAO

Table 2 Low monoamine oxidase activity in schizophrenia

Subtype	Paranoid schizophrenia
Symptoms	Auditory hallucination Negative symptoms in unmedicated males
Prognosis	Better social adjustment and fewer symptoms at follow-up (other study reported higher symptomatology in senium)

activity^[39,40]. In drug-free schizophrenic patients, only a minority of studies found a decrease in platelet MAO in patients compared to healthy controls, while most studies did not observe any difference between the groups^[38].

The inconclusive data regarding MAO activity reduction in schizophrenia and the heterogeneity of the disease led researchers to look at subgroups and specific symptoms of the disorder (Table 2). Several studies found that a significant decrease in platelet MAO activity was associated with the paranoid subtype^[41]. Others found correlation between the presence of auditory hallucinations and reduced MAO activity^[42]. Interestingly, a significant positive correlation was found between negative symptoms and platelet MAO activity in unmedicated male but not female schizophrenic patients^[43]. These findings were only partially replicable by other studies. Attempts to relate disease prognosis with MAO activity have mostly failed, as enzyme activity was not related to either prognostic scores or age at onset of illness^[44]. One study, however, showed that 36 patients with schizophrenia or schizoaffective disorders, who had had low platelet MAO activity, had significantly better social adjustment and fewer schizophrenic symptoms at several years follow-up^[45]. Another study showed that patients with low platelet MAO activity are most likely to continue to manifest schizophrenic symptomatology in senium^[46].

The controversial findings regarding platelet MAO activity in schizophrenia may, in part, stem from methodological differences as many factors can influence MAO activity. For example, mechanical stress to platelets, such as centrifugation speed, has been shown to significantly affect their MAO activity^[47]. Conditions affecting the hematopoietic system can also affect platelet MAO activity, as it was shown to be enhanced in megaloblastic anemia and reduced in iron deficiency anemia and was significantly correlated with mean platelet volume, platelet protein densities and protein content per platelet^[48]. MAO substrate concentration can also affect MAO activity, since it appears that some chronic schizophrenics have lower Michaelis-Menten constant (Km) or maximal velocity (Vmax). Interestingly, it was reported that as many as 75 percent of the studies used suboptimal substrate concentrations, which could have led to the low estimate of the MAO activity and erroneous comparisons between schizophrenia and normal groups^[49].

Despite numerous reports of decreased platelet MAO activity in schizophrenia, this finding has not been generally accepted^[50]. Twenty years of research trying to correlate MAO activity with genetics, medication, symptoms and prognosis led to inconsistent and sometimes nonrep-

Table 3 Platelet serotonin in schizophrenia

High platelet serotonin	Low platelet serotonin
Paranoid schizophrenia	Non-paranoid schizophrenia
Correlated with severity of auditory hallucinations	Correlated with lack of insight and with conceptual disorganization
Chronic active course	
Higher levels in spring in patients with positive symptoms	
Winter born patients	

licable results and therefore it could not be established as a biomarker for schizophrenia.

Serotonin

Human platelets possess organelles, whose function is closely related to that of 5-HT neurons, including an active transport system for 5-HT, binding sites for many drugs and neurotransmitters, dense bodies, which store 5-HT, and mitochondria expressing MAO-B^[17]. Investigators have used different techniques to examine platelet 5-HT in psychiatry. Among the most common measurements are platelet 5-HT concentration, platelet 5-HT receptor density and 5-HT uptake. Naturally, the first studies on the serotonergic system were in patients with affective disorder, but the therapeutic success of serotonergic/dopaminergic antipsychotic drugs has directed attention towards the role of 5-HT in schizophrenia. One study found that platelet serotonin concentrations were significantly elevated in patients with chronic schizophrenia and in patients with bipolar depression^[51]. Other studies showed that mean platelet 5-HT concentrations in patients with schizophrenia, mostly in paranoid schizophrenia and patients with psychotic depression, were higher than those of controls^[52,53]. Hyperserotonemia was positively correlated with severity of auditory hallucinations and negatively correlated with lack of insight and conceptual disorganization. Hyposerotonemia, although less common than hyperserotonemia, was present in nonparanoid schizophrenia and in nonpsychotic depression; in the same study they also found an increase in platelet 5-HT concentration in schizophrenia, especially in a subgroup with a chronic active course of the disease compared to normal controls^[53]. The gender differences in platelet 5-HT, with a significantly higher concentration in males than in females, were preserved in healthy and schizophrenia subjects^[54] (Table 3).

Contradictory findings were reported regarding the effect of antipsychotic drugs on platelet 5-HT. One study noted that antipsychotic drugs elevate blood 5-HT^[55], while others have reported that antipsychotic medication seemed to decrease platelet 5-HT^[56]. Other groups could not detect an association between any clinical feature or treatment and hyperserotonemia, except for significantly higher 5-HT levels in a subgroup of patients receiving benzodiazepines^[57].

Seasonal variations in platelet 5-HT concentrations were observed in schizophrenic patients, with higher lev-

els in spring in these patients compared with depressed patients and normal controls. Specifically, those changes were observed in patients with positive symptoms and clearly separated them from patients with negative schizophrenia. Birth season had no effect on 5HT levels in healthy subjects, while in patients with schizophrenia, birth-season had a significant effect, with highest levels observed in patients born in winter^[58]. Daylight duration was probably not involved in the latter phenomenon, as a recent study was unable to detect an association between platelet 5-HT concentrations and duration of exposure of schizophrenic patients to daylight^[59].

A complex relationship exists between the serotonergic system and the hypothalamic-pituitary-adrenal (HPA) axis^[60]. One study observed that schizophrenia patients with dysregulated HPA axis activity, manifested by a high rate of non-suppression of the axis following dexamethasone administration (dexamethasone suppression test-DST), also show hypercortisolemia and platelet hyperserotonemia independent of the duration of the disease. These results were repeated by several additional studies^[61]. In a recent study, however, a significant correlation between platelet 5-HT and plasma cortisol or plasma prolactin concentrations was observed in healthy controls, but not in schizophrenia or depressed patients^[62].

Studies on 5HT receptor binding revealed that, in unmedicated schizophrenic patients, the maximal number (B_{max}) of 5-HT_{2A} receptors was significantly higher than that of control subjects. Typical antipsychotic medication significantly decreased B_{max} values to a comparable level of the healthy controls^[63]. In contrast, another showed that treatment with the atypical, new generation antipsychotic drug risperidone, which blocks 5-HT_{2A} receptors with a higher efficiency, caused a significant increase in the 5-HT_{2A} receptors^[64]. Other groups found no significant difference between schizophrenic patients and normal subjects in the K_D of the 5HT receptors and showed that treatment with typical antipsychotic drugs, such as haloperidol or thiothixine, did not affect its B_{max} or K_D ^[65]. These findings are in line with differences found in the B_{max} of 5-HT₂ binding sites that disappeared after correction for age and sex. An exception was schizophrenic patients who made suicide attempts and showed significantly higher B_{max} than non-suicidal schizophrenic patients who did not differ from normal controls^[66].

Unlike major depression, in which numerous studies have proposed imipramine binding to 5-HT transporter as a biological marker for the disorder^[67,68], only a few studies were performed in schizophrenic patients. Some of them point at a tendency towards lower platelet 5-HT uptake in schizophrenia compared with healthy subjects^[69-71], while others found no change due to the disease^[71,72]. A more recent study found that the mean B_{max} of serotonin transporter sites for schizophrenic patients without antipsychotic therapy was significantly higher than in normal controls. The B_{max} values for schizophrenic patients on various antipsychotic drugs were significantly lower than those obtained from unmedicated

schizophrenic patients and were comparable to those found in normal control subjects. The K_D values in all subject groups remained unchanged^[73].

Additional neurotransmitters

The study of other neurotransmitter systems in platelets in schizophrenia is scarce, even although a plethora of evidence from pharmacological, molecular, genetic and imaging studies point to abnormalities in dopamine and glutamate transmission in this disorder. One study compared dopamine uptake in platelets before and after treatment with typical antipsychotic drugs. No difference was observed between drug-free patients and healthy subjects. However, following treatment with typical antipsychotic drugs, the K_m for platelet dopamine uptake increased by 76% in subjects with schizophrenia and decreased by 94% in subjects with non-schizophrenia psychoses^[74]. Despite these confusing findings, attempts were made to identify a circulating inhibitor of platelet dopamine uptake in plasma of schizophrenic patients, which failed^[75]. Glutamate receptor was also assessed using the intracellular calcium response to glutamate as a marker for its sensitivity. The response of the schizophrenic and depressed psychotic subjects to glutamate stimulation was significantly greater than control subjects ($P < 0.005$)^[76]. Therefore, in 2009 Baier *et al.*^[77] suggested a fast flow-cytometric method to investigate glutamate receptor sensitivity in whole blood platelets as a future diagnostic tool. Although the link between schizophrenia and alterations in the adrenergic system is not well documented, adrenergic receptors in platelets were studied as well. For example, Rosen *et al.*^[78] reported that schizophrenic patients with relatively subsensitive platelet α -2-adrenergic receptors, as measured by clonidine binding, tend to have more negative symptoms and a diminished clinical response to chlorpromazine.

Alongside the gastrointestinal tract, platelets are the major source of serotonin in the periphery. Therefore, it is conceivable to expect that some of the impairments in the serotonin system in the CNS in schizophrenia will also be manifested in the periphery, as has been observed for other mental disorders. Despite the prominent role of dopamine and glutamate in the pathophysiology of schizophrenia, the findings in platelets regarding both neurotransmitters are less convincing, probably since platelets are not a major anatomical substrate for these transmitters.

AGGREGATION, PROSTAGLANDINS AND ARACHIDONIC ACID

In schizophrenia, the issue of blood clotting and aggregation was brought to clinical attention by the increased incidence of mortality caused by cardiovascular disease and the increased risk of thrombotic complication in schizophrenic patients treated with antipsychotics. Unexpectedly, *in vitro* studies show that antipsychotic drugs reduced response of blood platelets to ADP, a stimulator of

platelet aggregation^[79,80]. It was suggested that the blockade of the 5-HT_{2A} receptors by the antipsychotic drugs is involved in the decreased platelet aggregation^[81]. In drug-free schizophrenic patients, aggregation of platelets stimulated by collagen or by serotonin was significantly lower^[82,83] and was negatively correlated with psychosis ratings^[84]. Yet aggregation by ADP showed increased response^[82] in unmedicated schizophrenic patients. It was also shown that the reduced collagen induced platelet aggregation remained decreased, despite clinical recovery following antipsychotic treatment^[83]. In contrast, there are reports on indistinguishable aggregation responses to ADP, adrenaline, 5-HT or collagen of platelets derived from unmedicated schizophrenics compared to healthy controls^[85].

Prostaglandins play a major role in platelet aggregation. Both prostaglandin deficiency^[86] and excess^[87] hypotheses have been proposed for the etiology of schizophrenia. In platelets, it was shown that ADP stimulates the synthesis of prostaglandin E1 (PGE1) in normal subjects and patients with affective illness but not in schizophrenic patients^[88]. An interesting finding was revealed by studies on the inhibitory effects of PGE1 on the platelet aggregation response to ADP in schizophrenia^[89-92]. The schizophrenic patients demonstrated hyposensitivity to PGE1, which was manifested by reduced PGE1-stimulated cAMP accumulation compared to normal controls, suggesting a hyposensitivity of the platelet PGE receptor in schizophrenia. Kanof *et al.*^[92] showed that platelet cAMP response to PGE1 was negatively correlated with global symptom severity and with several indexes of positive symptom severity, but not with negative symptom severity. Focusing on the clinical characteristics of the subgroup showing platelet PGE1 subsensitivity revealed relatively successful heterosexual relationships, less anergia and more severe activation factor, as analyzed by the Brief Psychiatric Rating Scale (BPRS). Notably, MRI studies in schizophrenia demonstrated negative correlation between platelet PGE1 subsensitivity and the corpus callosum size^[89]. Abnormalities in corpus callosum size and shape were observed in schizophrenia and suggested to be consistent with a hypothesis of decreased connectivity between the left and right hemispheres in the disorder^[93].

Prostaglandin abnormalities in schizophrenia may stem from impairments in the metabolism of arachidonic acid, which is the precursor of prostaglandins and is essential for neuronal membrane activity. Platelets were found to emit a burst of chemiluminescence during incubation with arachidonic or linoleic acid (an essential fatty acid, which can be used in the biosynthesis of arachidonic acid). This chemiluminescence response indicates activation of prostaglandin synthase. One study demonstrated that platelets from drug naive schizophrenic subjects showed significantly increased arachidonic acid metabolism compared to control subjects. No significant difference was observed between schizophrenic and control subjects in their chemiluminescence response to

linoleic acid. In schizophrenic subjects, treatment with antipsychotic drugs normalized the arachidonic acid overactive response, while linoleic acid response was unaffected^[94]. Concomitantly, additional study showed that the activity of platelet phospholipase A2 (PLA2), which releases arachidonic acid from membrane phospholipids, was significantly increased in schizophrenia compared to healthy subjects and to patients with other psychiatric disorders. Antipsychotic treatment significantly reduced PLA2 activity^[95].

The impairment in arachidonic acid metabolism can also stem from changes in the cytoplasmic membrane function and in the regulation of secondary messengers, for example, the phosphoinositide signaling system. This system is coupled to several neurotransmitter receptors in the central nervous system, stimulation of which induces phospholipase C (PLC) to catalyze the hydrolysis of plasma membrane phosphatidylinositol bisphosphate (PIP2) to inositol trisphosphate (IP3) and diacylglycerol^[96]. The latter can be converted to arachidonic acid by PLC. No differences in the content or in precursor incorporation into PIP2 were found in platelets of drug-free schizophrenic patients^[97]. Yao *et al.*^[18] proposed increased activity of PLC in schizophrenia, which resulted in increased production of the second messengers DAG and IP3, in response to thrombin, in normal control subjects as well as in schizophrenic patients before and after haloperidol withdrawal. Increase in IP3 and its binding to its receptors on the endoplasmic reticulum causes cytosolic concentration of calcium to increase. Indeed, Ríková *et al.*^[98] found increased cytosolic Ca²⁺ level in platelets in drug-free schizophrenic patients. Taken together, these data pinpoint arachidonic acid, which is a precursor for prostaglandins on one hand and an important component of cell membranes and major intracellular signaling pathways on the other hand, as a part of a continuum linking between neurotransmission dependent vulnerabilities and basic physiological changes, such as coagulation function. The recent interest in polyunsaturated fatty acids in schizophrenia may open new research directions in platelets in this disease.

OTHER NEW POTENTIAL BIOMARKER

Mitochondrial complex I

Mitochondria are the energy source that drives the biochemical processes involved in various cell functions, including neuronal activity. Neuronal activity can monitor synaptic connectivity associated with adaptive changes in emotional and cognitive function, all abnormal in schizophrenia. Several studies by our lab and by others showed mitochondrial dysfunction in schizophrenia. In platelets, an increase in the activity of mitochondrial complex I (COI) in medicated and unmedicated schizophrenic patients compared with control subjects and patients with affective disorders was observed^[99]. In patients, COI increased activity was positively correlated with psychotic symptomatology, while its decrease was observed in pa-

tients with residual schizophrenia^[100]. Upon combining imaging studies of brain glucose uptake in rest with platelet COI activity, a disease-state dependent correlation between glucose metabolism (rCGM) in schizophrenia-relevant brain areas and platelets COI was observed. No such correlations were observed in healthy subjects, suggesting the correlation between peripheral COI activity and rCGM as a pathological factor that is differentially expressed in subgroups of schizophrenic patients^[101]. Interestingly, abnormality in the expression of several subunits of COI and one of their transcription factors Sp1 was observed in platelets as well as in postmortem brain specimens of patients with schizophrenia^[102].

Platelet auto-antibodies

As part of the autoimmune theory of schizophrenia, one group showed that platelet auto-antibodies (PAA) titers were significantly higher in schizophrenia patients than those in the control group^[103]. Additional study showed positive correlation between social withdrawal retardation scores and the level of PAA and a negative correlation between PAA levels and depressive symptoms in chronic schizophrenic patients^[104]. These results provide evidence for the existence of distinct correlations between peripheral autoantibodies, total psychometric scores and discrete symptom clusters of schizophrenia (BPRS subscales).

Glutamine synthetase-like protein

Glutamine synthetase-like protein (GSLP) is a glutamate-metabolizing enzyme in human platelets. It was reported that GSLP in platelets was significantly higher in chronic patients with schizophrenia than controls. Interestingly, similar increases in GSLP levels were also observed in schizophrenic patients' prefrontal cortex, a brain area highly implicated in this disorder. Moreover, survival analysis of the group of patients chronically treated with the atypical antipsychotic drug olanzapine showed that the higher the level of platelets GSLP was before treatment, the shorter the treatment duration was required to achieve a positive clinical response^[105].

Genomics based research in platelets of schizophrenic patients

Only few studies implicate the recent genomic advances in schizophrenia in platelet research. A recent study showed that the Src-family kinase Fyn, which is involved in brain development and emotional regulation, was lower in platelets of schizophrenic patients and their first degree relatives^[106]. An additional study focusing on the disordered platelet phospholipid metabolism of schizophrenic patients found an association between PLA2 activity in platelets and the BanI of PLA2 reported in schizophrenic patients^[107]. None of the proteins of more replicable genes in schizophrenia, such as DISC1 and neuregulin, were mentioned in platelet research.

A scheme summarizing the main methods used for platelets research in psychiatry and the findings with the most prevalent tendency of change identified in platelets

Table 4 Main methods used in psychiatry platelet research

Method	Brief description and representative references
MAO activity measuring	2-carbon14-tryptamine hydrochloride or carbon14-benzylamine as substrates ^[16,109]
Platelet 5-HT levels	High-performance liquid chromatography (HPLC) with fluorimetric or electrochemical detection ^[110]
Serotonin transporter binding sites	[³ H] Imipramine binding assay ^[73]
Noradrenergic binding sites	Specific binding of ³ H-clonidine and ³ H-yohimbine to platelet membranes ^[111]
Prostaglandin E1 suppression of platelet aggregation response	Using PGE1 to suppress platelet aggregation in response to ADP ^[89]
Platelet Associated Antibodies 11	Enzyme linked immunoassay based on color development after reaction with anti-human immunoglobulin bound to horseradish peroxidase ^[112]
Platelet mitochondrial enzyme activity	Measuring different complexes of the respiratory system activity ^[100]

MAO: Monoamine oxidase; HPLC: High-performance liquid chromatography; PGE1: Prostaglandin E1.

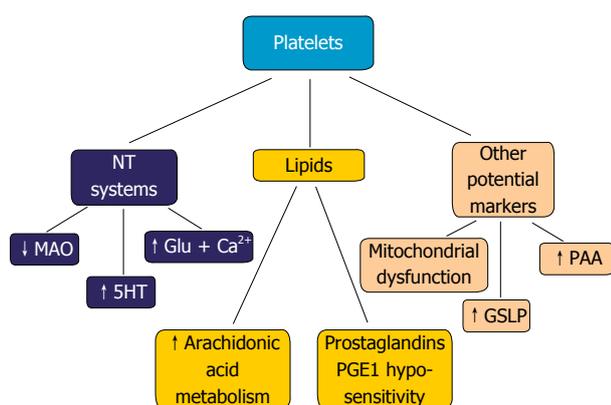


Figure 1 Schematic presentation of the main impairments observed in platelets of patients with schizophrenia. Glu: Glutamate; GSLP: Glutamine synthase-like protein; 5HT: Serotonin; MAO: Monoamine oxidase; NT: neurotransmitters; PPA: Platelet auto-antibodies.

of schizophrenic patients addressed in the present review is presented in Table 4 and in Figure 1.

CONCLUSION

The endeavor of platelet research in schizophrenia is a thrilling lesson about tendencies in the history of science. The psychopharmacological revolution raised hope to find a definitive answer for the long running debate about the biological origin for mental disorders. Platelet research that started in the 1950s was one of the tools for establishing the bioaminergic theory of depression, which inspired the dopaminergic theory for schizophrenia. The finding of low MAO activity in schizophrenic patients' platelets was a promising innovative tool that converges, in itself, scientific theory and clinical practice; reduced activity of an enzyme which is known to degrade dopamine in the central nervous system, which results in an increment of dopamine, in line with the dopaminergic theory prediction. MAO activity in platelets was expected to become a simple way for improving diagnostic methods, while the genetic and familial research was aimed at contributing to the development of prevention strategies. Hundreds of studies were published through the 70s and 80s but the inconsistency of the results led to a signifi-

cant fading in the number of publications on platelets in general and on platelet MAO activity in particular.

The question is whether there is justification for the relative desertion of platelet research, a field of research which probably will not give us the ultimate answer but still may shed some light on the biological abnormalities in mental disorders. It seems that the same psychological processes in the attachment of scientists to their theory fuel their disappointment from unfulfilled pretentious wishes. In psychiatry, the combination of the critics interpreting a biochemical model to a psychiatric disorder which seems extremely reductionist and the subjective diagnostic criteria with many overlaps that manifests in a high percentage of comorbidity, amplifies the motivation to find a biomarker. This can, as Wirz-Justice claimed, lead to "too many 'instant' unreplicable studies"^[108]. With the accumulating biological knowledge that entangled the old dopaminergic theory in schizophrenia, our wish to find a single marker for a single diagnosis seems further away than ever. However, totally disregarding the reported findings in platelets in schizophrenia bears the risk of throwing the baby out with the bathwater. An alternative is to make use of the following models: (1) One diagnosis - few biomarkers: equivalent and complementary to the diagnostic operational criteria for mental disorders (DSM-IV, ICD-10), one has to identify as many biomarkers as can be found in blood samples to support the clinical diagnosis; (2) Split diagnosis according to a single biomarker: define a set of clinical characteristics as a sub-diagnosis of schizophrenia that could be recognized by a single biomarker. For example, define a subgroup of schizophrenic patient with platelet PGE1 sub-sensitivity or altered mitochondrial functions; and (3) Biomarkers for symptoms: instead of characterizing the study groups using the current diagnosis criteria, patients' groups will be defined according to symptoms. For example, studies in the past that correlated the presence of auditory hallucinations and reduced MAO activity or psychotic symptoms and hyperserotonemia. Such markers will help to overcome the complexity of validating subjective symptoms that are currently used for diagnosis or, as many clinician claim, as targets for treatment.

In conclusion, the ample data of parallel findings in brain and in platelets of abnormalities in various biologi-

cal factors, such as mitochondrial related functions and GSLP, substantiate the relevance of platelets as proxies or a “peephole” to the inaccessible CNS and encourage further studies in platelets using modern, more sophisticated techniques. The latter should be based on analyses of an array of diverse biological factors that will serve to portray a profile of abnormalities, which will become a biomarker of this complex disorder.

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