Blood Platelet as a Peripheral Cell in Oxidative Stress in Psychiatric Disorders

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Abbreviations

ADAM	A disintegrin and metalloprotease
ADP	Adenosine diphosphate
AMPAR	Glutamate receptor
cAMP	Cyclic adenosine monophosphate
CGMP	Cyclic guanosine monophosphate
COX	Cyclooxygenase
DAG	Diacylglycerol
DAT	Dopamine transporter
DTS	Dense tubular system
EAAT	Excitatory amino acid transporter
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
GP	Glycoprotein
GPCRs	G protein-coupled receptors
GPX	Glutathione peroxidase
GSH	Glutathione
GSSG	Oxidized glutathione
HMWK	High molecular weight kininogen
IL	Interleukin
LIGHT	Cytokine
LOX	Lipoxygenase

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MAO	Monoamine oxidase
MDA	Malonyldialdehyde
MMP	Matrix metalloproteinase
MP	Microparticle
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
NOS	Nitric oxide synthase
OCS	Open canalicular system
PAF	Platelet-activating factor
PAR	Protease-activated receptor
PC	Phosphatidylserine
PDGF	Platelet-derived growth factor
PE	Phosphatidylethanolamine
PF_4	Platelet factor 4
PGH_2	Prostaglandin H_2
PKC	Protein kinase C
PKG	Protein kinase G
PLA_2	Phospholipase A_2
PLC	Phospholipase C
RANTES	Regulated on activation, normal T-cell expressed and secreted
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RSNOs	S-nitrosothiols
SOD	Superoxide dismutase
SSRI	Selective serotonin reuptake inhibitor
TBARS	Thiobarbituric acid reactive substance
TGF	Transforming growth factor
TIMPs	Tissue inhibitor of metalloproteinases
TNF	Tumor necrosis factor
TP	Thromboxane receptor
TXA_2	Thromboxane A_2
Tyr	Tyrosine
VASP	Vasodilator-stimulated phosphoprotein

1 Introduction

Excessive oxidative stress occurring in the brain may be reflected by abnormalities in oxidative processes in peripheral cells from patients with psychiatric disorders, and blood platelets may be useful as diagnostic markers and indicators of the progression of the disease and as a tool to develop therapeutic approaches monitoring the therapeutic efficacy (Bakken et al. 2006; Camacho and Dimsdale 2000; Da et al. 1988; Fisar and Raboch 2008; Freedman 2008; Plein and Berk 2001; Stahl 1977).

Although the brain is the major organ affected by psychiatric disorders, research indicates that other cell types in the body show changes in these diseases, and

studying the more readily accessible cell could provide important information about the disease progression.

Important pathogenic mechanisms are likely common to psychiatric disorders, and oxidative stress appears to be a trigger in the complex chain of events leading to psychiatric diseases (Ng et al. 2008). Enhanced production of reactive oxygen/nitrogen species (ROS/RNS) in aging and neurological or psychiatric diseases is not restricted to the brain, but can also be seen in several peripheral tissues. Oxidative/nitrative changes are not confined to the CNS but also occur in peripheral cells, especially in circulating blood platelets. Moreover, impaired cognitions are associated with oxidative changes in platelet constituents or altered platelet function. Excessive oxidative processes and oxidative stress, hallmark features of the brain, have also been shown to occur in other peripheral blood cells such as lymphocytes or red blood cells. Since the oxidative stress is a global phenomenon and the markers of oxidative cell injury in the CNS correlate with the markers in peripheral non-CNS material in animal as well as in humans, it has become a common practice to assess the extent of cellular oxidative damage in the CNS from analyses of peripheral indices of oxidative stress and resultant cell injury.

Peripheral lymphocytes are more difficult to purify compared to platelets or erythrocytes. The preparation of lymphocytes from anticoagulated blood requires several steps and contamination with other cell types, e.g., platelets in the range of 1–5 % cannot be excluded. Isolation and purification of small platelets from anticoagulated samples of the blood is much easier than lymphocytes, and in the isolation from blood platelet suspension, the contamination with leukocytes is less than one leukocyte in 10^6 platelets. Cultured skin fibroblast from patients is also used to provide information about psychiatric disorders especially in signal transduction (Mahadik and Mukherjee 1996). They are limited model since they lack nucleus and mitochondria used to determine the changes in membrane lipids or activities of antioxidative enzymes.

Platelets contain several receptors, intracellular signaling cascade components, and have long been utilized as peripheral model of receptor-mediated signal transduction mechanisms in the central nervous system (Stahl 1977; Mangano and Schwarcz 1981; Da et al. 1988; Barradas and Mikhailidis 1993; Plain and Burk 2001; Bakken et al. 2006; Camacho and Dimsdale 2000). Platelets are useful for discovering mechanisms that underlie the multiple changes in cell signaling pathways that accompany psychiatric disorders. Oxidative stress seems to be a convergence factor that leads to many psychiatric disorder-related changes (Plein and Berk 2001; Mahadik et al. 2001; Ng et al. 2008; Yao et al. 2004, 2006).

2 Blood Platelet Activation

Blood platelets derived from megakaryocytes are the smallest anucleated cells in the blood which are essential elements of primary hemostasis. They play important roles in several diverse processes beyond hemostasis, malignancy, and infection and by promoting inflammatory and immune response. They maintain vascular integrity

and contribute to wound healing (Brydon et al. 2006; McNicol and Israels 2008; Smyth et al. 2009; Horstman et al. 2010; Nurden 2011).

Individual platelets vary in terms of volume, density, and reactivity. Resting platelets are discoid with a diameter which averages 1–2 μm and a mean cell volume of around 5–6 fl. The normal platelet count is in the range of $150–350 \times 10^9$/L. Under normal conditions human platelets circulate in the bloodstream for approximately 8–10 days. They respond immediately to vascular injury and interact with exposed elements of the underlying connective tissue and rapidly change from discoid shapes to active round forms with filopodia and lamellipodia. Platelet cytoskeleton composed of actin and tubulin polymers maintains the shape of the resting and activated platelets. The shape change represents one of the earliest events (< 5 s) after platelet stimulation. In platelet cytoplasm there are few mitochondria and different granules, large amounts of glycogen as a source of energy and a complex membranous system consisting of an open canalicular system (OCS) which allows connections between cytosol and surrounding medium, and the dense tubular system (DTS) which stores metabolic enzymes and together with mitochondria is involved in metabolic processes and controls the cytosolic calcium (Blockmans et al. 1995; Kamath et al. 2001).

The platelet possesses three types of specific granules: alpha granules, dense granules, and lysosomes. The granules store numerous substances which are released after activation of platelets induced by different agonists (Blair and Flaumenhaft 2009; Horstman et al. 2010).

Activation of platelets is a process controlled via a multitude of biochemical events, ranging from receptor stimulation, intracellular signal transduction to platelet response: shape change, adhesion, aggregation, and secretion of active compounds stored in platelet granules (Li et al. 2010; Rivera et al. 2009).

The controlled platelet granule exocytosis is an essential part of platelet function leading to secondary amplification of ongoing platelet activation. Platelets are activated at sites of vascular injury by the combined effects of a number of molecules, including collagen, thrombin, ADP, serotonin, epinephrine, and thromboxane A_2 (TX A_2) that interact with specific platelet glycoprotein receptors. Platelet response to agonist includes reorganization of the actin cytoskeleton, secretion of compounds stored in platelet granules, exposure of integrin fibrinogen receptors (GPIIb/IIIa) on platelet surface membranes, and aggregation. Activated platelets alter the composition of their membranes resulting in the expression of P-selectin derived from the alpha granule membrane on the surface of the platelet. The exposure of P-selectin is especially important for platelet–leukocyte interaction. During platelet activation, microparticles (MPs) are released and catalyze the coagulation cascade. MPs may play an important role in hemostasis, neuroinflammation, and neurodegenerative diseases (Horstman et al. 2010). They express most of the platelet membrane proteins (proteomic studies revealed about 600 proteins) and can directly activate and bind to leukocytes. Proteomic has became a promising technology for platelet research. It is a method for analysis of the rapid changes in platelet protein organization during activation and aggregation (Zahedi et al. 2006). The initial steps of platelet activation are regulated by protein phosphorylation events. Phosphorylation of amino acid residues is mostly transient and can change rapidly upon activation or inactivation of phosphatases and

kinases by specific stimuli like cyclic adenosine monophosphate (cAMP) and Ca^{2+} (Coles et al. 2002; Nagai et al. 1994). Malfunctions of these enzymes can lead to pathological events. The phosphorylation of serine and tyrosine residues is a very important switch in the signaling. The level of phosphorylated proteins depends on the activities of kinases and phosphatases (Zahedi et al. 2006). The human platelet membrane proteome reveals several new membrane proteins acting as signal receptors, mediators, or enhancers (Moebius et al. 2005). The platelet possesses different receptors. G protein-coupled receptors (GPCRs) on platelet membranes are present with only a few hundred copies per cell, whereas the platelet integrin αIIbβ3 (GPIIb/IIIa) receptors are present with 500,000 copies per platelet. On activated platelets P-selectin is present with about 10,000 copies per cell (Moebius et al. 2005) and activation can change the level of receptor expression on platelets.

In activated platelets anionic phospholipids such as phosphatidylserine (PS) and phosphatidylethanolamine (PE) become exposed on the platelet surface and render the membrane procoagulant. In vivo, the most important aggregating agents (agonists) are collagen in the vessel wall, ADP from injured cells (red cells) or released from the platelet dense granules, and thromboxane A_2 formed from arachidonic acid by stimulated platelets and thrombin. Other agonists such as serotonin, epinephrine, norepinephrine, platelet-activating factor (PAF), and vasopressin may contribute to the aggregation and activation. Serotonin is a weak agonist and involves $5\text{-}HT_{2A}$ receptors which differ from the sites responsible for serotonin uptake. Platelets carry all the serotonin in the blood in their dense granules.

In the signaling pathways induced by a platelet agonist, the known effectors include phospholipase C (PLC), phospholipase A_2 (PLA_2), and phosphoinositide 3-kinase. PLC hydrolyses membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) to form 1,4,5-IP3 and diacylglycerol (DAG), which in turn raise the cytosolic free Ca^{2+} concentration and activate protein kinase C (PKC) isoforms. In platelets PLA_2 mobilizes arachidonic acid mainly from PC and PE, membrane phospholipids containing over 70 % arachidonic acid in the cell. Free arachidonic acid is converted via cyclooxygenase (COX) pathway to active thromboxane A_2 (Hamberg et al. 1975). Both TXA_2 (half-lives of 30 s) and its immediate precursor PGH_2 are labile potent stimulators of platelet activation and act on TP receptor (Armstrong 1996). Activated platelets acutely generate docosahexaenoic acid-containing phospholipids via lipoxygenase (12-LOX) pathway (Morgan et al. 2010).

Thrombin, within seconds, causes the increase in the cytosolic Ca^{2+} concentration triggering downstream Ca-dependent events, including activation of PLA_2. The activation of Ras superfamily members (Rc, Rao, Rap1b) takes place, leading to rearrangement of the actin cytoskeleton and shape change. Thrombin, like ADP or epinephrine, is able to inhibit adenylyl cyclase activity causing the decrease in cAMP level. Suppression of cAMP formation induced by other agonists plays an important role in platelet activation. The increase of cAMP (after prostacyclin or adenosine) inhibits platelet activation. cGMP as a second messenger activates PKG with phosphorylation of intracellular targets and inhibition of Ca mobilization, integrin GPIIb/GPIIIa activation, cytoskeleton rearrangement, secretion, and phosphoinositide 3-kinase (Radomski et al. 1987b, 1990; Gordge and Xiao 2010).

To respond to extracellular signals, platelets possess unexpectedly a large variety of surface receptors for stimulatory and inhibitory ligands, and platelet activation can change the level of receptor expression. There are three groups of platelet surface receptors with specific properties: G protein-linked receptors, enzyme-linked receptors, and ion channel-linked receptors. Thrombin activates platelets by proteolytic cleavage of protease-activated receptors (PARs). Human platelets express members of the Gq,G_{12}, and Gs family of G proteins and four of the Gi family, G_{11}, G_{12}, G_{13}, and Gz. Gq is the primary link to PLC beta activation. Gs and the three Gi family members stimulate and inhibit adenylyl cyclase activity in platelets. The activation of adenylyl cyclase by Gs is counterbalanced by the inhibitory protein Gi. Thrombin, ADP, epinephrine, and PAF stimulate platelets and at the same time lower cAMP concentration by activating G_1.

Thrombin interacts with platelet via a specific proteolysis of the extracellular N-terminal of PAR (proteinase-activated receptor), which leads to the exposure of a new tethered ligand, binding to the receptor and initiating signal transduction.

In platelets stimulated by strong agonists, arachidonic acid is released from membrane phospholipids by active $cPLA_2$ and rapidly converted by cyclooxygenase (COX) pathway into active TXA_2, a potent platelet agonist. The activity of $cPLA_2$ is regulated by at least two major mechanisms: translocation of $cPLA_2$ from cytosol and/or phosphorylation of Ser505 mediated by ERK 1/2. Aspirin inhibits platelet activation by inhibition of COX activity and reducing level of TXA_2. Thromboxane B_2, the stable metabolite of short-lived TXA_2, is the marker of platelet activation.

Different lipid mediators are generated during platelet activation: resolvins derived from omega-3 fatty acids via LOX pathway, PAF, eicosanoids and endocannabinoids. Endocannabinoids which include anandamide (*N*-arachidonoylethanolamine) and 2-arachidonoylglycerol (2-AG) are released from activated platelets and may activate these cells through endocannabinoid receptors present in platelets (Signorello et al. 2011). Human platelets express endocannabinoid receptors CB_1 and, to a lesser extent, CB_2 belonging to the superfamily of G protein-coupled receptors (Catani et al. 2010). 2-AG can be consider a new physiological platelet agonist. Anandamide at low concentrations, through PI3/AKT pathway activation, stimulates eNOS activity and increases NO level in platelets (Signorello et al. 2003). The ability of activated platelets to release 2-AG suggests that a chronic over-release of 2-AG by platelets may be a causal factor in the cognitive deficits associated with negative symptom in schizophrenia, and increased platelet activation may lead to the changes of endogenous cannabinoid level in the brain (Pryor 2000; Pandey et al. 2010).

Adenosine is an important regulatory metabolite and an inhibitor of platelet activation via binding of A_2 platelet receptor and the elevation of intracellular cAMP. The expression of A_2 adenosine receptor is induced by oxidative stress (Johnston-Cox and Ravid 2011).

Platelets synthesize proteins (COX, integrin, Fyn) and they have developed extranuclear mechanisms to process and efficiently translate mRNA into protein (Weyrich et al. 2009; Hattori et al. 2009). Moreover, the transcriptomic profile of platelets has begun to be studied. They contain NF-kB – a transcription factor which controls the gene expression of inflammatory mediators. The latter may be involved in platelet function (Beaulieu and Freedman 2009).

3 Blood Platelets in Inflammation

The traditional role of platelets as mediators of hemostasis and thrombosis is well documented. Increasing evidence suggests that activated platelets are involved in and may promote inflammation. They help maintain and modulate inflammation and are a major source of proinflammatory molecules such as P-selectin, CD40L, tissue factor, and matrix metalloproteinases (MMP_5) (Smyth et al. 2009; Horstman et al. 2010; Nurden 2011). Activated platelets release and express different inflammatory mediators. The adhesion of circulating platelets to the vascular endothelium is a key element of the proinflammatory and prothrombogenic states and is associated with oxidative stress: a variety of mechanisms are involved (Cooper et al. 2002; Urbich et al. 2002; Chakrabarti et al. 2005; Stokes et al. 2009).

Platelets as inflammatory mediators possess the major classes of factors active in inflammatory states. Platelet–leukocyte aggregation links hemostasis to inflammation. Horstman et al. (2010) suggest that platelets are active partners with leukocytes in the entry to the CNS, and PAF derived from platelets would facilitate opening of the blood–brain barrier in the microenvironment since PAF is involved in disruption of endothelial cell junctions.

The initial platelet–leukocyte contact is mediated by P-selectin which in activated platelets is rapidly translocated to the surface. In addition to P-selectin, platelets contribute to platelet–leukocyte aggregation by releasing microparticles. During platelet–leukocyte aggregation MMPs are liberated and present on the cell surface. Interaction between platelets and leukocytes can occur via P-selectin on the surface of activated platelets and PSGL-1 (P-selectin GP ligand-1, CD162) on leukocytes. High molecular weight kininogen (HMWK) can also form the bridges between GPIbα on the platelet and CD11b/CD18 (Mac 1) on leukocytes (Chavakis et al. 2003). From alpha granules, upon platelet activation, platelet factor 4 (PF_4, chemokine $CXCL_4$) in abundance other chemokines including RANTES and a variety of growth factors, PDGF, FGF, EGF, TGF-beta, VEGF, and IL-1, IL-8, IL-6, are released in abundance. Platelets after stimulation express on their surface CD40L, a member of the tumor necrosis factor (TNF) superfamily which is then cleaved and circulates as soluble sCD40L (Inwald et al. 2003; Santilli et al. 2007). The binding of sCD40L to platelet CD40 results in cell activation, expression of P-selectin on platelets, and subsequent binding of platelets to leukocytes (Stokes et al. 2009). Platelets are the main source of CD40L in the circulation (Pignatelli et al. 2004). LIGHT is another transmembrane protein belonging to the TNF family associated with platelets and released after activation. Platelet-derived LIGHT induces inflammatory responses in endothelial cells and monocytes (Otterdal et al. 2006).

Matrix metalloproteinases (MMPs) have been recognized as major factors participating in disruption of the blood–brain barrier (Horstman et al. 2010). MMPs comprise a family of zinc-dependent endopeptidases with differential proteolytic activity against various proteins of the extracellular matrix. In platelets five different MMPs such as MMP-1, MMP-2, MMP-3, MMP-9, and MMP-14 have been identified (Chung et al. 2004). ADAM-10, ADAM-17 (a disintegrin and metalloprotease), ADAMTS13 (ADAM with thrombospondin domain), and TIMPs (tissue inhibitor of metalloproteinases) are present. MMP-1 and MMP-2 may prime

platelets for adhesion and aggregation (Chung et al. 2004). The release and action of platelet MMPs are regulated by nitrite oxide (NO) (Martinez-Cuesta et al. 2001). MMPs play an important role in the migration of immune cells to sites of inflammation by degrading basement membranes and extracellular matrix components. During platelet–leukocyte aggregation NO and free radicals are released (Cooper et al. 2002). NO and MMP-1, MMP-2, MMP-3, and MMP-9 play an important role in the regulation of PAR agonist-induced platelet–leukocyte aggregation (Chung et al. 2004).

Thornton et al. (2010) have identified platelets as a key source of IL-1α. It indicates that platelet activation and platelet-derived IL-1α are major contributors to inflammation-mediated injury in the brain.

4 Changes of Platelet Structure and Function in Psychiatric Disorders

The diversity of platelet components is implicated in psychopathological states, and platelets are important tools for psychopharmacological research since they offer an interesting vantage point for understanding the neurophysiology processes of various psychiatric disorders as well as their association with cardiovascular diseases. Several data support the role of oxidative stress in diverse psychiatric disorders such as bipolar disorder, depression, autism, schizophrenia, and anxiety disorders; however, the broadest data regarding oxidative stress mechanisms have been derived from studies in schizophrenia (Table 1).

Similarities between platelets and neurons are particularly important with respect to serotonin metabolism (Lesch et al. 1993). Since serotonergic neurons and platelets express serotonin-related enzymes, receptors, and transporters, the alterations in the CNS are likely to be reflected in platelet levels of the same molecules. Abnormalities of the platelet serotonergic system have been found in major depression, schizophrenia, seasonal affective disorder, obsessive–compulsive disorder, posttraumatic stress disorder, panic disorder, eating disorders, aggressive behavior, substance use, autism, and Alzheimer's or Parkinson disease (Mikuni et al. 1991; Yao et al. 1996; Yamawaki et al. 1998; Khait et al. 2002; Ljubicic et al. 2007; Chen 2009; Nemeroff and Owens 2009; Safai-Kutti et al. 1985). Moreover, various parameters of the serotonergic system in platelets undergo seasonal fluctuation (Khait et al. 2002; Ljubicic et al. 2007).

Platelet 5-HT_{2A} receptors are coupled to PLC through Gq proteins, and their stimulation induces generation of IP_3 and DAG. The platelet 5-HT_{2A} receptor (a serotonin postsynaptic receptor in the brain) is a common object of study (Kovacic et al. 2008; Velayudhan et al. 1999). 5-HT level is elevated in platelets of autistic individuals. Platelet hyperserotonemia has been detected in 25–60 % of autistic children, and a significantly higher level of 5-HT_{2A} receptor mRNA in platelets has been revealed which could suggest serotonin system dysregulation (Hranilovic et al. 2009; Kazek et al. 2010). Serotonin is involved in many of the same processes affected by cannabinoids (Janusonis 2008; Zvetkova et al. 2010). 5-HT uptake by

Table 1 Markers of oxidative stress in blood platelets and changed platelet reactivity in patients with some psychiatric disorders

Schizophrenia	Decreased activities of antioxidant defense system	Reddy et al. (1991); Dietrich-Muszalska et al. (2005)
	Platelet lipid peroxidation, platelet protein nitration/carbonylation, decreased thiol and GSH level	(Dietrich-Muszalska and Olas 2009a)
	Reduced cAMP in platelets	Kafka et al. (2009)
	Increased activity of platelet PLA2	Gattaz et al. (1995)
	Overactivity of COX	Das and Khan (1998)
	Alteration in platelet function: increased aggregation, secretion	Yao et al. (1992, 1994); Dietrich-Muszalska and Olas 2009b; Dietrich-Muszalska 2008)
	Alteration in membrane composition	du Bois et al. (2005)
Drug-naive, first-episode schizophrenic patients	Elevated expression of platelet integrin receptors	Walsh et al. (2002)
	Supersensitive platelet glutamate receptors	Berk et al. (1999, 2000); Baier et al. (2009)
Depression disorder	Ultrastructural changes in platelets	Palmar et al. (1997)
	Increase platelet reactivity and alterations in platelet function	Bruce and Musselman (2005); Celano and Huffman (2011); Wittstein (2010)
	Increased level of PGE2, TXA2	Lieb et al. (1983); Zafar et al. (2010)
	Increased platelet reactivity	Celano and Huffman (2011); Chen (2009)
	Increased platelet aggregation, P-selectin expression	Mendoza-Sotelo et al. (2010)
	Supersensitive glutamate receptors	Berk et al. (2001)
Bipolar disorder	Changes in glutamate uptake	Do Nascimento et al. (2006)
	Decreased PKC changes in platelet signaling	Pandey et al. (2008)

platelets was significantly increased in a group of chronic marijuana smokers suffering impairment of cognitive function, and the activity of 5-HT transporters was affected by cannabinoids at high concentrations. It seems that a lowered 5-HT uptake may reflect gender-related differences in effects of psychoactive cannabinoids (Velenovska and Fisar 2007).

Depressed patients appear to have more platelet receptors compared with healthy volunteers and exhibit higher platelet activation and enhanced procoagulant properties than healthy control (Palmar et al. 1997; Nemeroff and Owens 2009). Abnormalities in inositol phosphate signaling system in platelets can be used as diagnostic marker for psychiatric disorders including major depression (Dwivedi and Pandey 2009; Panday et al. 2010).

Platelets possess some key components of functional dopaminergic system including the dopamine transporter (DAT) and dopamine receptor D_2 (Frankhauser

et al. 2006). Dopamine can potentiate ADP-induced platelet adhesion. Platelets store acetylcholine, and acetylcholine esterase is present indicating platelet cholinergic system. Platelet monoamine oxidase (MAO) activity has been evaluated in several neuropsychiatric disorders indicating the higher activity in parkinsonian and demented patients but lower in alcoholics. Platelet MAO is solely of B type (Magos 2002).

In the etiology of various psychiatric diseases such as depression, schizophrenia, ADHD, and addiction, monoaminergic dysfunction is involved, and platelets may well serve as an easy accessible peripheral system to study monoaminergic neurotransmission that is controlled by rapid and selective reuptake of neurotransmitters by specific transport proteins: DAT, SERT, and NED (Frankhauser et al. 2006; Zalsman et al. 2011).

Glutamate metabolism is also modified in platelets from patients with psychiatric disorders (Berk et al. 1999, 2000, 2001; Do Nascimento et al. 2006; Baier et al. 2009). Platelets express glutamate uptake transporters (EAATs) to clear glutamate from the blood where its concentration is relatively high and vesicular glutamate (VGLUT) transporter to load glutamate into platelet dense granules. Platelets express both mRNA and proteins for the three major glutamate transporters, namely, EAAT1, EAAT2, and EAAT3 (Zoia et al. 2004). Platelets store and release glutamate during platelet activation (Berk et al. 2000; Berk et al. 2001; Begni et al. 2005; Do Nascimento et al. 2006; Morrell et al. 2008). Platelets express glutamate receptors AMPARs that have a functional role in regulating platelet agonist response. Morrell et al. (2008) demonstrated the importance of glutamate as a modulator of platelet function. In platelets the presence of AMPAR subunit protein $GluR_1$ has been described (Chen 2009). This type of AMPA receptor could play a role in comorbid depression and cardiovascular disease. NMDA receptor signaling is involved in the regulation of platelet production from megakaryocytes. Platelet glutamate receptors are supersensitive in schizophrenia and depression with psychotic disorders. Glutamate uptake by platelets may be modified in parallel with mood changes in the subjects. Platelets from patients with bipolar I disorders with manic episodes have an increased uptake of glutamate compared to platelets from control subjects. The glutamatergic system is modulated by oxidative stress induced by heavy metals (Borges et al. 2007).

In platelets from schizophrenic patients, reduced level of cAMP (Kafka et al. 1979; Kaiya et al. 1990), overactivity of COX (Das and Khan 1998), elevated expression of integrin (Walsh et al. 2002), increased phosphatidylinositol pathway (Yao et al. 1992), and platelet activation (Yao et al. 1994) are described. The increased activity of platelet PLA_2 (Gattaz et al. 1995), changed membrane lipids (Horobin 1996), depressed expression of protein signaling (Hattori et al. 2009), and changed antioxidant defense with oxidative alteration in platelet molecules, especially membrane lipid peroxidation (Mahadik et al. 2001; Dietrich-Muszalska et al. 2005, Dietrich-Muszalska and Olas 2009a), are also present. Oxidative modification of platelet membrane phospholipid composition may lead to the alterations in neurotransmitter systems in psychiatric disorders, especially in schizophrenia,

where omega-3 and omega-6 polyunsaturated fatty acid levels are reduced (Horrobin 1996; Du Bois et al. 2005). Numerous neurotransmitter systems are sensitive to ROS (Sah et al. 2002; Nakamura and Lipton 2011).

Several lines of evidence support the hypothesis that imbalance between the production of ROS and the detoxification of reactive intermediates is a feature of psychiatric disorders, and oxidative stress may play a functional role in these disorders. Psychiatric disorders are characterized by a lower antioxidative defense system, higher free radical production, and improvement of some symptoms after antioxidant administration (Ng et al. 2008; Tsaluchidu et al. 2008; Schedel et al. 2010). Oxidative stress leads to the modulation of vascular homeostasis (Zho et al. 1999). In psychiatric disorders, when excess of ROS/RNS production together with oxidative stress is observed, the biomolecules (lipids, proteins, nucleic acids) present in plasma and blood cells are modified. Measurement of levels of markers of oxidative stress reflects a status of increased oxidative stress. Alterations in oxidative processes in the brains of patients with psychiatric disorders may also occur in non-neuronal tissues including fluids such as cerebrospinal fluid, plasma, urine, and blood cells. In platelets from schizophrenic patients, oxidative damage was present (Reddy et al. 1991; Yao et al. 2001). In platelets from patients with schizophrenia of paranoid type, a significantly low thiol level in platelet proteins was observed (Dietrich-Muszalska and Olas 2009a), and oxidative stress in platelets from schizophrenic patients seems to be associated with the oxidation of free protein thiols to disulfides. It may be the consequence of oxidation/nitration process (Essex and Li 2003; Kalyanaraman 2004).

Modifications caused by ROS/RNS in platelet proteins from schizophrenic patients include not only oxidation of thiol groups but also protein carbonylation and nitration of tyrosine. Nitric oxide and its metabolites may have a role in the pathophysiology of schizophrenia (Bernstein et al. 2005). Peroxynitrite generated from NO and superoxide anion can induce oxidation of proteins measured by the level of carbonyl groups and nitration of some amino acid residues, particularly tyrosine. A stable product of tyrosine nitration is measured as a biomarker of protein modifications caused by peroxynitrite or other RNS. Nitration of tyrosine residues in platelet proteins results in the alteration of protein structure and function and, usually, inhibition of activity of enzymes. Moreover, nitration of tyrosine may directly inhibit the tyrosine phosphorylation involved in signal transduction pathways in platelets (Ischiropoulos 1996). Dietrich-Muszalska and Olas (2009a) provide evidence that in platelet proteins from patients with schizophrenia, in acute period of psychosis, a high level of 3-nitrotyrosine is present. The measurements of abnormalities in oxidative processes in peripheral cells such as platelets from patients have the potential to be useful as diagnostic markers, as indicators of the disease progression, as a tool to develop therapeutic approaches, and as monitors of therapeutic efficacy. Platelets are also useful for discovering mechanisms that underlie the multiple changes in cell signaling pathways that accompany psychiatric diseases and lead to the alteration of platelet function, mainly hyperactivation of platelets and cardiovascular diseases.

5 Modification of Platelet Function Induced by ROS and RNS

Platelets are influenced by ROS in multiple types of pathology based on inflammation, endothelial cell damage, or thrombosis (Radomski et al. 1987b; Cooper et al. 2002; Olas and Wachowicz 2007; Freedman 2008; Forstermann 2010). The platelet activation cascade is a complex process with different cellular signaling pathways, and ROS produced mostly intracellularly are involved in cellular signaling and may act as second messengers (Krotz et al. 2004; Begonja et al. 2006; Essex and Li 2006; Essex 2009; Savini et al. 2010; Sill et al. 2007; Manickam et al. 2011; Shamova et al. 2011). ROS and RNS play a very important role in platelet activation, since they may modulate the signal transduction in various and sometimes opposite ways affecting different platelet metabolic pathways (Blackmore 2011; Handin et al. 1977; Morrel 2008; Radomski et al. 1987a; Rodrigues et al. 2010; Patel et al. 1999; Krotz et al. 2004; Freedman 2008). ROS may regulate platelet function by reducing $^{\cdot}$NO bioavailability because ROS scavenge platelet or endothelium-derived $^{\cdot}$NO (Hirata et al. 1995; Matsubara et al. 2003; Munzel et al. 2003). Rapid reaction between $^{\cdot}$NO and superoxide anion leads to the generation of peroxynitrite which is a potent nitrating and oxidizing agent and may modify platelet structure and function (Beckman and Koppenol 1996; Bermejo et al. 2005; Moro et al. 1994; Practico and Violi 1997; Olas and Wachowicz 2007; Wachowicz et al. 2008). Even small increase in these radicals, particularly superoxide anion ($O_2^{\cdot-}$), may cause a remarkable peroxynitrite generation (Huie and Padmaja 1993; Pryor and Squadrito 1995). $^{\cdot}$NO produced in endothelial cells or in platelets interacts with $O_2^{\cdot-}$, leading to the reduction of vasorelaxation and platelet activation. Increased concentration of $O_2^{\cdot-}$, especially during inflammation, is one of the factors controlling the half-life of $^{\cdot}$NO. Platelets themselves can generate several ROS/RNS including superoxide anion (Jahn and Hansch 1990; Wachowicz et al. 2002), hydrogen peroxide (H_2O_2) and hydroxyl radical (Pratico et al. 1999), nitric oxide (Radomski et al. 1987b; 1990), and peroxynitrite (Olas and Wachowicz 2007).

In stimulated platelets the aggregation of platelets is accompanied by the burst of H_2O_2 (Maresca et al. 1992; Iuliano et al. 1994, 1997; Pignatelli et al. 1998; Hedin and Fowler 1999). H_2O_2 is involved in platelet activation cascade (Del Principe et al. 1985, 1991; Salvemini and Botting 1993; Ambrosio et al. 1994). ROS regulate tyrosine phosphorylation in integrin subunit responsible for aggregation (Irani et al. 1998; Hernandez-Hernandez et al. 1999).

Blood platelets synthesize $^{\cdot}$NO (Signorello et al. 2003; Leoncini et al. 2005), and platelet NO synthase (NOS) has been described (Muruganandam and Mutus 1994; Mehta et al. 1995; Sase and Michel 1995). Platelet activation leads to stimulation of NOS which in turn generates NO (Freedman et al. 1997). Protein kinase C may regulate NOS activity by direct serine/threonine phosphorylation (Hirata et al. 1995; Matsubara et al. 2003). In platelets $^{\cdot}$NO activates the soluble guanylyl cyclase and thereby increases intracellular cGMP (Munzel et al. 2003; Lohmann and Walter 2005; Marjanovic et al. 2005; Begonja et al. 2006; Marcondes et al. 2006). Inhibition

of integrin GPIIb/GPIIIa enhances the release of NO (Chakrabarti et al. 2004). NO inhibits platelet activation and the NO/cGMP pathway is a well-established mechanism of platelet inhibition. The inhibition of ROS production in platelets might lead to increase of cGMP and VASP (vasodilator-stimulated phosphoprotein) serine phosphorylation when more NO is present (Butt et al. 1994). Nitration of VASP, a protein critical for actin cytoskeletal rearrangement, may be important in the regulation of platelet aggregation (Sabetkar et al. 2002, 2008). Platelet superoxide anion can be converted to H_2O_2 by platelet superoxide dismutase SOD. H_2O_2 serves as a substrate for the production of hypochlorous acid by means of neutrophil myeloperoxidase.

The biological events triggered by signaling stimuli involve ROS, but it is not clear exactly what the molecular targets of ROS in signal transduction mechanisms are. Brill et al. (2009) hypothesize that oxidative damage could directly suppress platelet function by loss of platelet glycoprotein receptors (GPIbα, GPV). Oxidative stress activates tumor necrosis factor alpha (TNF_a)-converting enzyme (TACE/$ADAM_{17}$) and induces shedding of GPIbα and GPV on platelets. TACE activation is dependent on p38 mitogen-activated protein kinase signaling (Brill et al. 2009). Targets of ROS are G alpha proteins (Nishida et al. 2000).

After stimulation platelets produce superoxide anion mainly via NAD(P)H oxidase (Krotz et al. 2002; Begonja et al. 2006) and xanthine oxidase (Miller et al. 1993) which participates in signaling leading to integrin $\alpha_{IIb}\beta_3$ receptor activation and may act by other mechanisms than scavenging $^{\cdot}NO$. Ligand–receptor activation triggers a signaling cascade leading to ROS production which in turn enhances expression and activity of Ecto-NOX1. NAD(P)H oxidase-derived $O_2^{\cdot-}$ flux is in the nanomolar range and is similar to the flux that is present in endothelium cells, but less than <1 % of the amount of $O_2^{\cdot-}$ from activated neutrophils. Thrombin and collagen are thought to act in part via NAD(P)H^- oxidase-dependent intraplatelet oxygen radical generation, and the $O_2^{\cdot-}$ generated seems to be a particular link to integrin activation. Significant amounts of $O_2^{\cdot-}$ aside from NAD(P)H oxidase are generated during arachidonate cascade (Jahn and Hansch 1990). Since platelet-derived O_2 is a functionally relevant scavenger of platelet-derived $^{\cdot}NO$, it is possible that intraplatelet iron via iron-dependent oxidants would provide the redox conditions for the generation of further radicals such as hydroxyl radicals from H_2O_2 and lipid peroxides (Olas and Wachowicz 2005). Hydrogen peroxide does not evoke the activation of integrin receptor for fibrinogen, although both H_2O_2 and $O_2^{\cdot-}$ are produced within activated platelets. Hydrogen peroxide acts as a signaling molecule, and serine phosphorylation of VASP induced by H_2O_2 has been observed (Sabetkar et al. 2008). It induces platelet Ca mobilization, PKC activation, and phosphorylation of tyrosine (Juliano et al. 1994; Hedin and Fowler 1999; Gopalakrishna and Jaken 2000). Collagen stimulates intraplatelet H_2O_2 production which serves as an intraplatelet second messenger but alone is incapable to activate the integrin receptor (Del Principe et al. 1985, 1991; Pignatelli et al. 1998).

ROS participate in platelet activation (Maresca et al. 1992; Salvemini and Botting 1993; Ambrosio et al. 1994; Iuliano et al. 1997; Komiya et al. 1999; Olas et al. 2009; Pratico et al. 1999). On the other hand, platelets represent a relevant target for the action of exogenous ROS derived from the vascular wall. Enhanced ROS release

from the vessel wall can indirectly affect platelets (Forstermann 2010). Under inflammatory conditions platelets are also exposed to phagocyte-dependent production of high quantities of ROS. There are enzymes responsible for the reduction of free radicals and ROS. H_2O_2 is relatively stable and diffuses through membranes. In vitro exogenous H_2O_2 inhibits ADP-induced platelet aggregation but enhances platelet activation induced by collagen or arachidonate. Plasma possesses a variety of antioxidants that have effects on the level of different mainly vessel wall-derived ROS. Plasma redox state is altered by several plasma thiols such as cysteine and homocysteine and endogenous and exogenous antioxidants derived from diet. Homocysteine may change the redox state in platelets (Olas et al. 2008). Endothelial dysfunction or damage by oxidants is associated with enhanced risk for platelet activation (Cooper et al. 2002; Forstermann 2010).

In platelets NO is produced in the cytosol, in about 100 fmol NO/mg of platelet proteins. In unstimulated platelets ˙NO generation is about 4–7 pmol/min/10^8 platelets and increased to 11–21 pmol/min/10^8 platelets after activation (Mehta et al. 1995; Radomski et al. 1996; Zhou et al. 1995; Krotz et al. 2004). ˙NO-mediated reactivity depends mostly on the formation of secondary intermediates such as peroxynitrite and nitrogen dioxide than ˙NO per se. Peroxynitrite is a transient species with a biological half-life of 1–10 ms, shorter than of NO (1–30 s) (Radi 2004).

An elevated production of NO for prolonged periods of time in many pathological states, including psychiatric disorders, contributes to oxidative damage of different cellular macromolecules. NO is produced in stimulated platelets (Mehta et al. 1995; Zhou et al. 1995; Pignatelli et al. 2006), but collagen may decrease NO synthesis (Leoncini et al. 2005). A key oxidant and nitrating agent responsible for oxidation and nitration of platelet biomolecules leading to their altered function is peroxynitrite. It is an inflammatory mediator and its amount depends on the competition for superoxide dismutase and NO (Bartosz 1996). NO effectively competes with SOD for scavenging of superoxide. Platelets are very sensitive to low amounts of peroxynitrite which increases the levels of 3-nitrotyrosine in platelet proteins (Ischiropoulos and Gow 2005; Ischiropoulos 1998; Naseem et al. 2000; Reiter et al. 2000), oxidizes tryptophan in proteins (Kato et al. 1997), and alters protein structure and function (Ischiropoulos and Al-Mehdi 1995; Mondoro et al. 1997; Ducrocq et al. 1999; Bruckdorfer 2001; Low et al. 2002; Ischiropoulos 2003; Ischiropoulos and Gow 2005). Its effects may be also linked to platelet eicosanoid formation (Zhou et al. 1995; Boulos et al. 2000) because peroxynitrite inhibits cyclooxygenase via nitration of tyrosine residue (Tyr 385) and reduces synthesis of eicosanoids, especially TXA_2, a potent lipid mediator of platelet activation and vessel constriction. Platelets contain high level of CO_2 (~1 mM) and thiols (5 mM) which react with peroxynitrite. The reaction of glutathione with peroxynitrite produces a relatively stable S-nitroglutathione (Lufrano and Balazy 2003), whereas carboxynitrite is highly unstable. Peroxynitrite appears to possess a dual effect on platelet activation: it can inhibit or stimulate this process (Brown et al. 1998; Ducrocq et al. 1999; Olas et al. 2004a, b; Nowak and Wachowicz 2001a, b, 2002). Its inhibitory effect is probably caused by the formation of S-nitrosothiols (Radomski et al. 1992; Mayer et al. 1995; Gaston 1999; Crane et al. 2002; Gordge and Xiao 2010). Peroxynitrite is a

potent oxidative and nitrative species, and due to its ability to nitrate tyrosine, it affects cellular processes in the platelet dependent on tyrosine phosphorylation. The altered signaling cascades in platelets may be dependent on the complex effects of peroxynitrite on the activity of various kinases and phosphatases (Liaudet et al. 2009; Minetti et al. 2002).

Platelets express antioxidant enzymes, superoxide dismutase SOD, glutathione peroxidase GPx, and catalase that can not only prevent cytotoxic effects of ROS but also regulate by ROS signaling pathways in platelets. In addition to its antioxidant properties, GPx enhances the bioavailability of NO by catalyzing its liberation from S-nitrosothiols and reducing lipid peroxide.

Platelet ROS generation estimated by means of specific markers of oxidative stress such as 3-nitrotyrosine (Khan et al. 1998), lipid peroxidation (measured usually as TBARS – thiobarbituric acid reactive substances, or level of malonyldialdehyde MDA), free thiols, GSH, and carbonyl groups in protein (Dalle-Donne et al. 2003a, b; Wong et al. 2010) could potentially be used as a marker and a predictor for the progression of psychiatric diseases.

The defense mechanisms against RNS, especially peroxynitrite, are crucial for platelet function. Plant antioxidants (polyphenols) present in human diet or selenocompounds may protect blood platelets against toxicity of peroxynitrite (Arteel et al. 1999; Klotz and Sies 2003; Olas et al. 1999, 2004, 2006).

Numerous transmitter systems are sensitive to ROS. Exogenous ROS may interact with receptors and transporters and alter ligand–receptor interaction or ion transport indirectly via actions within the lipid environment of the platelet membranes. ROS are raised in both physiological and pathological processes (psychiatric disorders), but efficient mechanisms have evolved for their detoxification. Increased oxidative stress was described in platelets from chronic smokers (Takajo et al. 2001). Platelet redox state may be influenced by the alteration of vascular redox state, the presence of endogenous and exogenous antioxidants, and the formation of ROS and RNS that the defense mechanisms against RNS/ROS are unable to counterbalance. ROS, by directly affecting the redox state, modulate platelet function.

5.1 The Effects of ROS/RNS on Platelet Thiols

The oxidation of the protein thiols to mixed disulfides is an early cellular response to oxidative stress. S-nitrosothiols (RSNOs) are compounds produced by the S-nitrosation of thiols, usually cysteine (Nakamura and Lipton 2011). They act as NO donor agent via cGMP or cGMP-independent mechanisms of their action, including prevention of TXA_2 synthesis, nitration of alpha actinin, and inhibition of ADP receptors ($P2Y_{12}$). RSNOs regulate protein disulfide isomerase (Gordge and Xiao 2010).

ROS/RNS, especially peroxynitrite, oxidize GSH producing oxidized glutathione (GSSG) and decrease the equilibrium between reduced and oxidized glutathione (GSH–GSSG ratio) in the platelet (Quijano et al. 1997; Nowak et al. 2003). This ratio is very important for the redox regulation of protein thiols (Giustarini et al. 2000;

Schafer and Buettner 2001; Essex 2009). The majority of protein thiols exist in reduced form, when the GSH–GSSH ratio is high. *N*-acetyl-L-cysteine is able to restore intraplatelet free thiols and shifts the redox balance favor of GSH concomitant with the inhibition of platelet aggregation. The GSH–GSSG ratio in platelets seems to be one of the potentially important regulators of platelet signaling. *N*-acetylcysteine a glutathione precursor reduces ROS generation associated with the increase of intraplatelet GSH (Berk et al. 2008; Dean et al. 2011; Gibson et al. 2009).

Several glycoprotein receptors in platelets such as GPIb and GPIIb/GPIIIa contain thiol groups which are extracellular redox-sensitive sites. Various forms of redox modulations of thiols or disulfides in platelet glycoprotein receptors exist. These include modification by low molecular weight thiols such as reduced glutathione or homocysteine and oxidized glutathione or by NO derived from S-nitrosothiols. Levels of these redox compounds are changed in various disease states, and in some cases physiological concentration of these compounds may modify platelet responsiveness (Essex and Li 2003, 2006). Moreover, platelets themselves contain a trans-plasma membrane redox system capable of reducing extracellular disulfide bounds. In the blood a redox homeostasis exists and redox environment is controlled. Changes in the extracellular redox state induced by diseases or pharmacological agents that modify the platelet redox environment will modify platelet function (Schafer and Buettner 2001; Crane et al. 2002). Redox-sensitive sites in the platelet such as vicinal thiols in GPIIb/GPIIIa involved in platelet aggregation can be regulated from the extracellular or cytoplasmic environment (Manickam et al. 2011). Extracellular redox state can also induce changes of the cell surface glycocalyx (Shamova et al. 2011). Since many biological processes are regulated by redox reactions that involve surface thiols, the extracellular redox state can have an important influence on disease status and may be a target for therapeutic interventions. Specific nitrosative or oxidative modifications of thiols in platelets may modulate platelet function (Minetti et al. 2002). Thiol-based reactions occur in proteins involved in platelet function, especially in extracellular platelet proteins, not only integrin receptors for fibrinogen but also in collagen receptors (integrin $\alpha_2\beta_1$) on platelets. They are regulated by protein disulfide isomerase and thiol metabolism. In the blood, low molecular thiols regulate redox state by converting disulfide bonds to thiols (Essex and Li 2003; 2009).

Blood platelets contain several organelles and proteins necessary for apoptotic processes and are able to undergo apoptotic events. Moreover, a number of apoptotic markers of nucleated cells have also been recognized in platelets, including markers of both receptor and mitochondrial pathways with executioner caspases, suggesting that anucleated platelets may undergo programmed cell death (Lopez et al. 2007) and ROS generated in the platelet are involved in apoptotic events. Platelets can display phosphatidylserine on their surface, produce microparticles, induce mitochondrial membrane depolarization, and activate caspases. Platelets modified oxidatively/nitratively by peroxynitrite can undergo apoptosis (Wachowicz et al. 2008). Peroxynitrite causes the activation of caspase-3; induces depolarization of mitochondrial membrane potential, microparticle formation, and PS exposure; and may be responsible for the activation of intrinsic pathways of apoptosis in platelets.

6 Platelet Activation and Cardiovascular Events in Psychiatric Disorders

There is considerable epidemiological evidence supporting the association between depression and coronary heart disease where blood platelets play the central role in both acute and chronic coronary syndromes (Maes et al. 1996; Bruce and Musselman 2005; Wittstein 2010).

Depression is associated with increased platelet reactivity. Platelets share many biochemical similarities with neuronal monoamine system, particularly in the uptake, storage, and metabolism of serotonin. Serotonin participates in hemostasis by inducing platelet aggregation; therefore, therapy with selective 5-HT reuptake inhibitors (SSRIs) which modulate platelet activation and may protect platelets from hyperaggregability seems to be responsible for the reduction of cardiovascular mortality in major depression, where hyperaggregability of platelets is observed. Citalopram (SSRI) specifically inhibits collagen-induced platelet aggregation, secretory process, and expression of P-selectin on platelet membrane (Tseng et al. 2010). Platelets chronically medicated with SSRI exhibit lower platelet 5-HT content and reduced platelet aggregation induced by ADP, collagen, and epinephrine, but not arachidonic acid. This may explain the increased bleeding risk associated with SSRI treatment as well as beneficial effect of SSRIs in the prevention of myocardial infarction. It appears that SSRI may modulate platelet reactivity by an independent pathway different from GPIIb/GPIIIa inhibitors and antioxidants (Serebruany et al. 2001). SSRIs may represent an optimal class of dual agents treating depression and simultaneously inhibiting platelet reactivity Bismuth-Evenzal et al. (2012).

It has been proposed that serotonin-mediated platelet activation may be a key pathogenic link between depression and coronary heart disease. Platelets from patients with depression release from their granules PF4, B-thromboglobulin and P-selectin (Mendoza-Sotelo et al. 2010; Fisar and Raboch 2008). The activated integrin receptors for fibrinogen and the generation of thromboxane A_2 have also been demonstrated (Lieb et al. 1983). Zafar et al. 2010) studied the effects of both depression and anxiety on serotonin- and epinephrine-mediated platelet reactivity in a patient population with stable coronary artery disease. The authors have suggested that anxiety may be a better predictor of platelet reactivity than depression; however, the combination of depression and anxiety that frequently coexists resulted in greater serotonin-mediated platelet activation than depression alone (Zafar et al. 2010). Larger studies are necessary to determine whether depression and anxiety have independent effects on platelet reactivity.

Anorexia nervosa is a serious psychiatric disorder associated with significant cardiovascular mortality. Pereira et al. (2010) observed that aggregability of platelets from adolescents with anorexia nervosa was unchanged, whereas platelet NOS activity was reduced and cGMP unchanged. They hypothesized that alteration of L-arginine–NO–cGMP pathway in platelets may be early predictors of the incidence of cardiovascular disease in adult life.

In cardiovascular patients under platelet therapy (clopidogrel, aspirin), close monitoring of platelet function is recommended, especially when they are also under treatment with antipsychotic drugs.

7 Conclusion

Psychiatric nosology depends primarily on identifying syndromes, and a peripheral marker that reflects a specific disorder would have important clinical implications either diagnostically or as a measure of disease process. It seems that redox states in platelets that partly reflect the oxidative stress in the brain together with the changes of platelet function may predict or correlate with treatment outcome in some psychiatric disorders.

The results indicate the importance of the platelets in obtaining an insight into the changes in neurotransmitter function.

The neuron functions as part of a complex nervous network and it is not directly affected by changes in the blood, whereas the blood platelet has no direct connection with the nervous system, has a relatively short half-life (about 10 days), and is directly influenced by changes in the blood and vessel wall. Moreover, a major advantage in studying the blood platelet lies in its ease of access in patients.

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