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TOPIC HIGHLIGHT

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Influence of mental stress on platelet bioactivity

Pia Koudouovoh-Tripp, Barbara Sperner-Unterweger

Pia Koudouovoh-Tripp, Clinic for Biological Psychiatry, Department of Psychiatry and Psychotherapy, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria
Barbara Sperner-Unterweger, Clinic for General Psychiatry, Department of Psychiatry and Psychotherapy, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria
Author contributions: Sperner-Unterweger B and Koudouovoh-Tripp P contributed equally to this work.
Correspondence to: Pia Koudouovoh-Tripp, MD, Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria. pia.koudouovoh-tripp@uki.at
Telephone: +43-512-50423691 Fax: +43-512-50424778
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Abstract

It is well established that various mental stress conditions contribute, or at least influence, underlying pathophysiological mechanisms in somatic, as well as in psychiatric disorders; blood platelets are supposed to represent a possible link in this respect. The anculeated platelets are the smallest corpuscular elements circulating in the human blood. They display different serotonergic markers which seem to reflect the central nervous serotonin metabolism. They are known as main effectors in haematological processes but recent research highlights their role in the innate and adaptive immune system. Platelets are containing a multitude of pro-inflammatory and immune-modulatory bioactive compounds in their granules and are expressing immune-competent surface markers. Research gives hint that platelets activation and reactivity is increased by mental stress. This leads to enhanced cross talk with the immune system *via* paracrine secretion, receptor interaction and formation of platelet leucocyte-aggregates. Recently it has been demonstrated that the immune system can have a remarkable impact in the development of psychiatric disorders. Therefore platelets represent an interesting research area in psychiatry and their role as a possible biomarker has been investigated. We review the influence of mental stress on what is termed platelet bioactivity in this article, which subsumes the mainly immune-modulatory activity of platelets in healthy volunteers, elderly persons with chronic care-giving strain, patients with cardiovascular diseases who are prone to psychosocial stress, as well as in patients with posttraumatic stress disorder. Research data suggest that stress enhances platelet activity, reactivity and immune-modulatory capacities.

Key words: Mental stress; Caregiving strain; Posttraumatic stress disorder; Cardiovascular disease; Serotonin; Platelet activation; Platelet bioactivity

Peer reviewer: William Davies, PhD, MRC Centre for Neuropsychiatric Genetics and Genomics, Neuroscience and Mental Health Research Institute, Schools of Medicine and Psychology, Cardiff University, Henry Wellcome Building, Heath Park Campus, Cardiff CF14 4XN, Wales, United Kingdom

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PLATELETS IN PSYCHIATRY

Numerous studies have shown a relation between chronic mental stress conditions with some of the most disabling psychiatric and somatic disorders such as depression and cardiovascular diseases[1-4]. Platelets have been proposed to be a link between mental stress conditions and psychiatric or somatic disorders, as they have been shown to contain the largest amount of serotonin (5-HT) outside the central nervous system, as well as to express serotonin receptors 2A and 3A (5-HT-2A receptor, 5-HT-3A

receptor) and the serotonin transporter (SERT)[5]. The serotonin metabolism and turnover of platelets is supposed to resemble that of the central nervous system in their major kinetic features[6,7].

In addition to the importance of the serotonergic system in psychiatric disorders, recent observations indicate a major role of the immune system in the pathophysiology of psychiatric disorders[1,8-11]. For example, studies have shown an association between elevated circulating pro-inflammatory cytokines[12], and increased levels of peripheral adhesion molecules[13] due to depression. Moreover, patients with posttraumatic stress disorder (PTSD) display signs of immune activation[14-17] and alterations of the serotonergic and noradrenergic neurotransmitter systems[18].

The prominent function of platelets in hemostasis and thrombosis is well known, but further research on platelets has demonstrated that they are also part of the immune regulatory mechanisms[19-23]. Therefore, platelets are an even more attractive line of approach in psychiatry research due to their possible patho-physiological influences and their possible role as biomarkers. It has also been suggested that platelets may provide a patho-physiological link between acute and chronic stress and stress-related psychiatric or somatic syndromes[24-27].

This review focuses, on the one hand, on platelet activity in mental stress conditions in healthy young subjects, in an elderly population and in patients with cardiovascular disease and, on the other hand, on platelet activity in patients with a mainly stress-induced psychiatric disease, namely PTSD.

PLATELET ANATOMY AND ACTIVATION

Platelets are the smallest corpuscular blood components originating from megakaryocytes in the bone marrow. Resting platelets are of discoid shape and usually circulate in the periphery for approximately 10 d, until they are cleared by the spleen. Platelets contain three different types of storage granules (α granula, dense bodies, lysosomes) which include a vast majority of pro-inflammatory and immune-regulatory cytokines and adhesion molecules[19,28,29]. The dense bodies contain adenosine triphosphate (ADP), ATP, calcium and serotonin. ADP is a prominent mediator in reinforcing platelet activation, whereas serotonin is a weak platelet agonist with vasoconstrictive potential[30-32]. The α granules contain mainly pro-inflammatory and immune-modulatory molecules[30,33] like P-selectin, platelet factor 4 (PF-4), β-thromboglobulin (β-TG), RANTES, CD40, CD40L, as well as adhesion molecules ICAM, VCAM and PECAM[19,34,35], while the lysosomes contain clearing factors such as cathepsins, collagenase, and glycohydrolases[36].

Platelet activation can be initiated *via* different mechanisms, such as soluble agonists (e.g., thrombin, TXA2), shear stress, physical and mental stress[5,37,38]. Catecholamines, which are the main neurotransmitters in the stress response system, activate platelets *via* α2 and β2 adrenergic receptors[5,39,40]. It is important to differentiate between the degree of platelet activation in response to a stimulus, namely the platelet reactivity, and the duration of platelet activation, namely the platelet activation state. On activation, platelets are able to express certain surface markers such as the active form of the glycoprotein receptor GP Ⅱb/Ⅲa, p-selectin and CD40 ligand and to secrete the pro-inflammatory and immune-modulatory content of their storage granules[37]. This paracrine secretion is termed *platelet bioactivity* and enables platelets to cross-talk with other platelets, immune cells and endothelial cells[41,42]. Platelet aggregation following platelet activation is marked by a shape change that gives platelets the ability to bind fibrinogen *via* the active form of the surface glycoprotein GP Ⅱb/Ⅲa receptors[37]. These expressed activation markers are cleaved, promoting the circulation of soluble CD40L and soluble P-selectin. Molecules like CD40 and CD40L, members of the TNF super family, take on an important immune-modulatory role. This immune-regulatory dyad is able to enhance antigen presentation and to augment adaptive immune response[43]. CD40 and CD40L have the ability to influence the T-cell-dependent isotype switching of B-cell-produced antibodies and to enhance dendritic cell activation[44]. P-selectin promotes arteriosclerotic processes by a formation of platelet-leukocyte aggregates (PLAs) and interaction with endothelial cells[21]. PF-4 and β-TG are essential in leukocyte chemotaxis and activation[45].

LIFE STYLE AND DISEASE-RELATED FACTORS INFLUENCING PLATELET ACTIVATION

Platelet activation is known to be influenced by various lifestyle factors, such as smoking, dietary habits (especially the intake of alcohol, caffeine and caffeinated beverages) and exercise.

These variables have been intensively investigated, often with conflicting results[46]. Concerning the influence of exercise on platelet activation, it seems that duration and intensity of exercise play an important role. Strenuous exercise in sedentary men seems to have the most prominent impact[47,48]. As a further possible activating mechanism, an increase in catecholamine levels and shear stress are discussed[46]. Moderate alcohol intake has been observed to reduce platelet reactivity to agonists in contrast to strong alcohol consumption[46,49-52]. In healthy young smokers, an increase in P-selectin expression has been observed compared to non-smokers[46,53]. In line with this finding, different studies have reported smoking-induced elevations of P-selectin and β-TG levels[54,55]. Conflicting results have been found regarding the influence of coffee consumption on platelet reactivity[46].

Female hormones were reported to have a significant influence on serotonin receptors in the first half of the menstruation cycle[56,57], as well as on the enhancement of the SERT activity[56]. In addition, serotonin parameters

are affected by seasonal changes, with increased numbers of serotonin receptors in spring and autumn[58-60].

A large number of drugs are able to influence platelet activity, namely β blockers[61], other antihypertensives like calcium antagonists[62], α blockers, antidepressants such as SSRIs[63-65], MAO inhibitors[66], statins[67], aspirin and other NSAIDs, as well as anti-platelet and anti-coagulatory medication. It has to be noted that the effect of aspirin is detectable for at least 10 d, representing the duration of platelet turnover[68]. Because of the widespread use of benzodiazepines, it should be remembered that platelets express a peripheral benzodiazepine receptor[69].

In addition, an association between a variety of medical conditions and increased platelet activity, for example inflammatory bowel disease[70], diabetes[71,72] rheumatoid arthritis[73], arteriosclerosis[74], hypertension[75,76], and arterial fibrillation[77] has been reported. In diabetes patients, hyperglycemia and low-grade inflammatory processes have been reported to induce elevated levels of soluble P-selectin and CD40L[78-81]. Hypercholesterolemia has been found to increase platelet reactivity and activation state; it is supposed that its probable mechanism is a sensitization of platelets for agonists[82].

PLATELET ACTIVATION ASSESSMENT

The ability of platelets to adhere, be activated, and aggregate, allows the assessment of their reactivity and activation state[83]. Platelets are prone to activation by sampling procedures and laboratory techniques. This review focuses on platelet bioactivity; mechanisms of adherence and aggregation are not considered here.

In recent years, FACS analysis has emerged as an important technique for the assessment of platelet activation using surface activation markers such as P-selectin, the active form of GP Ⅱb/Ⅲa and the formation of PLAs. FACS activation marker analysis can be performed in whole blood, using only a very small amount of sample. As such, extensive sample processing, which in itself could lead to platelet activation, can be avoided[84]. P-selectin rapidly mediates platelet binding to circulating leukocytes *via* P-selectin GP ligand 1, which contributes to the formation of PLAs[83]. Therefore, PLAs are suggested to be a very sensitive marker of platelet activation *in vivo*[83].

A number of platelet pro-inflammatory and immunemodulatory secretory compounds such as PF-4, P-selectin and β-TG, can be measured in plasma, serum or sonicated platelets. Serum thromboxane B2 serum or urinary 11-dehydro thromboxane B2 levels can be assessed. Thromboxane B2 is a platelet cyclooxygenase-1 dependent metabolite of thromboxane A2 and reflects platelet activation[85].

Measurement can be performed by enzyme-linked immune assays or radio-ligand immune assays (RIA). These methods are associated with a variety of technical difficulties that may contribute to conflicting results. Preparing blood samples for these immunological assays makes them vulnerable to *in vitro* platelet activation[83]. Another limitation is the short half-life of the various compounds and the fact that PF-4, β-thromboglobulin and soluble p-selectin are not exclusively produced by platelets[83], whereas 95% of the soluble CD40 ligand is derived from platelets.

PLATELET ACTIVATION DUE TO MENTAL STRESS IN HEALTHY INDIVIDUALS AND ELDERLY PERSONS

Stress induces hypothalamic-pituitary-adrenal (HPA) axis hyperdrive and leads to a functional alteration of the central sympathetic and serotonergic system, possibly *via* neurotransmission influenced by a corticotrophin-releasing factor[2]. This HPA axis overactivity is sustained by activation of the inflammatory response system through mental stress[1,2].

The effect of mental stress tasks - mental arithmetic or cold pressor test - on platelet bioactivity PF-4 and β-TG[86] has been assessed in healthy young men. A significant influence of stress tasks, resulting in an increase in PF-4 and β-TG, was observed[86].

Two studies have investigated the effect of acute psychological stress tasks on the formation of PLA in healthy men. Hamer *et al*[87] chose a longitudinal design to determine a habituation effect in full-time employees who were assessed twice within 4 wk. Hamer *et al*[87] and Steptoe *et al*[88] evaluated PLA formation due to acute mental stress and recovery (up to 75 min) in healthy men according to their socioeconomic status. In both studies, participants' feelings about test difficulty, performance, controllability, and feelings of stress were also evaluated. PLA formation and the PLA subset formations of platelet-monocyte aggregates[87,88] and platelet-neutrophil aggregates[88] were assessed by FACS. A significantly increasing effect of mental stress tasks on PLA formation was observed[87,88]. Regarding the stress recovery period, PLA reached the highest levels 30 min post-stress, returning to baseline at 75 min. Socioeconomic status did not have a significant influence on stress responsivity as measured by PLA, but lower socioeconomic status was associated with higher baseline PLA[88]. No habituation effect was observed[87]. Hamer *et al*[87] provide a good methodological investigation for a possible habituation effect in stress tasks. Steptoe *et al*[88] evaluated platelet activation in the post-stress period for up to 75 min, which seems to be an adequate time-range for healthy men. Both studies collected their data in healthy young men.

Aschbacher *et al*[89,90] conducted four different studies on platelet reactivity in elderly persons. In dementia caregivers, which is an established paradigm of chronic mental stress, the effect of additional acute mental stress in combination with depressive and anxious symptoms or hormone replacement therapy (HRT) was investigated in a cross-sectional design. Two longitudinal studies were

also performed to assess the effect of acute mental stress in an elderly population without caregiving strain[91] and in dementia caregivers in combination with persistent depressive symptoms[92].

Pre-existing medical conditions and medications were assessed and controlled for or included in the analysis as confounding factors. The administered psychosocial evaluation instruments are presented in Table 1. The acute stress task was a three-min impromptu speech about an interpersonal conflict, namely the stolen belt paradigm[93], or a conflict involving a disreputable car salesman[94]. In the studies involving dementia caregivers, blood was drawn three times [at rest (baseline), immediately after stress task (reactivity), and 14 min post-stress (recovery)]. In the studies involving the elderly population, blood was drawn twice (at rest and immediately post-stress). Platelet outcome parameters were assessed by FACS. Two studies assessed platelet reactivity and recovery using P-selectin expression as activation marker[89,91]. The two other studies additionally assessed the percentage of platelet aggregates formed, as well as the percentage of fibrinogen-binding receptors (FbR) expressed[90,91]. Dementia caregivers displayed significantly higher levels of depression, anxiety, and overload scores. The presence of symptoms of depression and anxiety in caregivers was strongly associated with increased P-selectin reactivity and delayed P-selectin recovery; it was also significantly predictive for P-selectin reactivity. In non-caregivers, the use of antidepressants was significantly associated with decreased P-selectin reactivity[89]. The authors provide an excellent model for the study of interaction between acute and chronic stress and mood symptoms, and its effect on platelet reactivity in a cross-sectional and a longitudinal design. Caregivers on HRT showed a significantly delayed recovery of platelet activity[90]. The acute mental stress test showed a significant increase in all platelet outcome values at each time point in elderly volunteers[91]. The percentage of aggregates showed an increase of 15%, the percentage of FbR 22%, and the percentage of P-selectin a nearly 5-fold increase in the acute mental stress condition. The use of aspirin, antidepressants and statins influenced platelet activity. The authors provide robust data on platelet reactivity to acute stress in an elderly population. The subjects were predominantly Caucasian women, and different stress tasks were used; a possible task-dependent effect was not evaluated[91].

CARDIOVASCULAR DISEASES AND STRESS

In the late 1990s, two studies investigated the effect of hostility as a chronic mental stress condition on platelet reactivity in patients with preexisting cardiovascular diseases[95,96] (Table 2). Plasma β-TG levels[95] and GP Ⅱb/Ⅲa receptor activation were measured[96]. The investigations observed that hostility was significantly related to higher β-TG reactivity and increased platelet activation index markers, such as GP Ⅱb/Ⅲa activation and fibrinogen binding[95,96].

Recent studies evaluated the effect of acute mental stress on platelet activation in different groups of cardiovascular disease patients. Investigations were conducted in coronary artery disease patients with scheduled or accomplished coronary angiography or cardiological intervention[97-99] as well as in stable angina pectoris patients[100] and in patients who survived acute coronary syndrome[101] (Table 2).

Strike *et al*[101] aimed to evaluate the effect of acute emotional stress with regard to the onset of acute coronary syndrome. For this purpose, participants were retrospectively categorized in two groups (non-trigger group, emotional-trigger group), taking into account the experience of acute negative emotions two hours prior to the onset of cardiovascular symptoms. Various mental stress tasks were used: mental arithmetic[99], the paced auditory serial addition task[97], the Stroop colour word conflict test[98-102], anger recall[99], a public speech task[101] and the mirror tracing task[98]. The applied outcome measurements were plasma β-TG[99,100], plasma PF-4[97,100], a platelet activation marker set (e.g., GP Ⅱb/Ⅲa expression, P-selectin expression, mononuclear cell (MNC)-bound activated platelets)[99], and the degree of overall PLA formation, as well as the assessment of subset formations of platelet-monocyte and platelet-neutrophil aggregates[98,101]. PLA formation was monitored for 75 min[98] or 120 min post-stress[101]. No impact of acute mental stress on PF-4 levels was registered[97,100]. The results regarding β-TG were inconsistent; Wallén *et al*[100] showed a significant increase and Reid *et al*[99] found no significant change. Concerning the observed platelet activation markers in coronary artery disease patients, the acute mental stress task induced a significant increase in GP Ⅱb/Ⅲa expression, P-selectin surface expression, percentage of platelets positive for P-selectin expression, and percentage of activated platelets bound to MNC[99]. Regarding PLA levels, a significant effect of acute stress was observed in patients with acute coronary syndrome and an emotionally triggering event (e.g., emotional trigger group)[101]. These values returned to baseline after two hours[101]. Previous results showed an increase in PLA formation in response to the acute stress tasks in cardiovascular disease patients, as well as in healthy controls; however, PLA levels in the patient group were significantly higher 75 min post-stress[98].

Bacon *et al*[97] designed an elaborate stress protocol to evaluate the effect of various stressors thought to trigger cardiovascular events on multiple cardiovascular and platelet activation outcome parameters. Consideration was also given to the disease severity, which did not affect platelet activity. An accumulating effect of the different stress tasks might be possible. PF-4 was assessed in plasma, which is known to produce inconsistent results. Reid *et al*[99] investigated the stress-induced platelet activation using a broad marker set in a large patient group. The participants were predominantly men. Platelets were

Table 1 Effects of acute mental stress and chronic care-giving strain on platelet reactivity

Author	Study design	Comorbidities	Medication allowed and health behavior	Stress task and assessment inventory	Sampling and Analysis	Platelet reactivity	Result
Patterson *et al*[86] 1995	Acute mental stress and cold pressor test on platelet activity in healthy stress (22) *vs* no-stress group (5)	None		Rest 1 10 min mental arithmetics Rest 2 2.5 min cold pressor test	Rest 1 mental task Rest 2 cold pressor task	PF-4 β-TG	Mental arithmetics : ↑PF-4 ($P < 0.001$) and β-TG ($P < 0.001$) *vs* baseline Cold pressor test: ↑PF-4 ($P < 0.001$) and β-TG ($P < 0.001$) *vs* baseline
Hamer *et al*[87] 2006	Acute mental stress in full-time employees Longitudinal design 91 non-smoking men (33.2 yr average)	None		3 min role speech task 5 min mirror tracing task	Baseline 10 min post-stress FACS	% PLA % PMA	↑PLA and ↑PMA by trial ($P < 0.001$) and session ($P = 0.020$) *vs* baseline
Steptoe *et al*[88] 2003	Acute mental stress in men regarding socioeconomic status, cross sectional design 15 men with higher socioeconomic status *vs* 20 lower socioeconomic status	None	No aspirin allowed No coffein No caffeinated beverages No alcohol No exercise before testing	Stroop Colour Word Interference Test Mirror tracing task	Baseline imm post-stress 30 min post-stress 75 min post-stress FACS	% PLA % Plt-mo agg % Plt-ly agg % Plt-ne agg	↑PLA ($P < 0.009$), ↑PMA ($P < 0.037$), ↑Plt-ne-agg ($P < 0.045$) over trial *vs* baseline, greater number of overall PLA ($P = 0.031$) in lower social status *vs* higher, ↑PLA ($P < 0.001$) and Plt-ne-agg ($P = 0.003$) in both groups in stress *vs* baseline
Aschbacher *et al*[92] 2009	Acute mental stress in CG +/- persistent depressive symptoms, longitudinal design 99 CG (73 yr average, 68% female, 93% Caucasian)	Myocardial infarction Others not specified	Aspirin Antidepressants after enrollment: β-blocker	3 min impromptu speech Brief Symptom Inventory	Baseline imm post-stress (reactivity) 14 min post-stress (recovery) FACS	% P-sel exp	Persistent DEP predicted P-sel reactivity and recovery ($P < 0.01$) *vs* transient DEP
Aschbacher *et al*[91] 2009	Acute mental stress in elderly persons, longitudinal design 149 elderly participants (mean age 71 yr, 30% male, 93% Caucasian)	Myocardial infraction Diabetes Hypertension Hypercholesterolemia Cerebrovascular incident	Aspirin, antidepressants, statins, NSAIDs, anti-hypertensives, β-blockers, HRT, anti-aggregation drugs, anti-platelet drugs	3 min impromptu speech	Baseline imm post-stress FACS	% plt agg % FbR exp % P-sel exp	↑All platelet ($P < 0.001$) outcome measures in stress *vs* rest
Aschbacher *et al*[89] 2008	Acute mental stress in CG +/- negative effect Cross-sectional design 39 care-givers *vs* 31 non care-givers	Cerebrovascular disease Coronary artery disease Diabetes Hypercholesterolemia Hypertension CVD condition	Aspirin, antidepressants, α blockers, after enrollment: β-blocker	3 min impromptu speech Role overload scale	Baseline imm post-stress 14 min post-stress FACS	% plt agg % FbR exp % P-sel exp	↑P-selectin reactivity ($P < 0.001$), delayed P-selectin recovery ($P = 0.039$) in CG with DEP *vs* non-CG
Aschbacher *et al*[90] 2007	Acute mental stress on CG women +/- HRT Cross-sectional design 51 CG women (24 HRT) *vs* 27 non-CG (15 HRT)	Coronary artery disease Cerebrovascular disease Diabetes Hypercholesterolemia Hypertension	Aspirin, NSAIDs, antidepressants, anti-platelet drugs, antihypertensives, statins	3 min impromptu speech	Baseline imm post-stress (reactivity) 14 min post-stress (recovery) FACS	% plt agg % FbR exp % P-sel exp	HRT x CG effect on recovery of AGG ($P = 0.025$), P-sel ($P = 0.013$), FbR ($P = 0.012$); CG +HRT delayed post stress recovery of AGG ($P = 0.038$) and P-sel ($P = 0.004$) *vs* NCG + HRT, no CG effect among non-HRT

%: The percentage of; PF-4: Platelet factor 4; β-TG: β-thromboglobulin; PLA: Platelet-leukocyte aggregates; PMA: Platelet-monocyte aggregates; Plt-mo: Platelet-monocyte aggregates; Plt-ly: Platelet-lymphocyte aggregates; Plt-ne: Platelet-neutrophil aggregates; P-sel: P-selectin; CG: Care-giver; non-CG: Non care-giver; HRT: Hormone replacement therapy; CG X HRT: Interaction between care-giving stress and hormone replacement therapy; AGG: Aggregates; FbR: Fibrinogen binding receptor; DEP: Depressive symptoms; Plt: Platelet; Mo: Monocyte, Ly: Lymphocyte; Ne: Neutrophils; Exp: Expression; NSAIDs: Non steroidal anti-inflammatory drug; FACS: Fluorescence-activated cell sorting; imm: Immediately.

Table 2 Effects of mental and physical stress on platelet reactivity of patients with cardiovascular disease

Author	Study design	Comorbidities	Medication allowed and health behavior	Stress task and assessment inventory	Sampling	Platelet outcome parameters	Results
Markovitz *et al*[95] 1996	Hostility and stress task in post MI-patients Cross-sectional design 14 stable post-MI *vs* 15 age matched healthy men	Not specified	Sublingual nitro, no calcium-channel blockers or platelet inhibitors for 10 d, NSAIDs for 10 d, no β-blockers for 48 h	Structured Interview Type A behavior and "Potential for Hostility" Speech Task "Cook-Medley Hostility" Scale BDI Paffenberger Questionnaire Spielberger State Anxiety Inventory	Baseline Post-stress task	β-TG	↑β-TG (P = 0.006) in healthy controls *vs* post-MI, correlation of ↑levels of Type A and ↑β-TG reactivity (P = 0.02)
Markovitz *et al*[96] 1998	Hostility in patients with CHD Cross sectional design 32 non-smoking patients *vs* 23 non-smoking healthy controls aged 45 to 73 yr	Not specified	Sublingual nitro statins, no aspirin/anti-platelet medication for 14 d, no oral or topic nitrates for 48 h, no calcium channel blockers for 48 h, no SSRIs	Type A Structured Interview BDI	Wound incision 1 min after incision 2 min after incision	Wound induced fibrinogen receptor activation indicators FbR activation FbR binding FACS	Relationship between hostility and FbR activation at 2 min and FbR binding at 1 min (P = 0.02) in CHD patients *vs* healthy controls
Reid *et al*[99] 2009	Acute mental stress in CAD patients requiring coronary angioplasty Cross sectional design 249 patients (15, 3% women)	Diabetes Hypertension Previous MI Previous PCI	Diabetes hypertension, aspirin, ACE inhibitors, β-blockers, topical or oral nitrate statins, clopidogrel	Mental arithmetics Anger recall BDI Maastricht Questionnaire STAEI Cook-Medley Hostility short-form PSS	Baseline imm post stress	GP Ⅱa/Ⅲb expression % of MNC bound plt P-sel expression % of P-sel expression β-TG FACS ELISA	↑GP Ⅱb/Ⅲa (P = 0.002), ↑% of MNC bound plt (P = 0.01) and ↑P-sel (P = 0.005) in stress *vs* baseline, ↑% of plt P-sel (P < 0.01) in stress *vs* baseline
Bacon *et al*[97] 2006	Acute mental and acute physical stress in CAD patients with elective cardiological intervention Cross-sectional design 72 patients (57 men, 15 women)	Hypertension Hyperlipidemia Diabetes Smokers	Aspirin/copidrogrel, ACE-inhibitors, β-blockers, calcium-channel blockers, diuretics, nitrates, statins, antidiabetic medication	Rest 1 8 min Paced Auditory Serial Addition Rest 2 8 min submaximal exercise test	Rest 1 post task Rest 2 post task	PF-4 ELISA	Mental stress: PF-4 ns changes *vs* baseline, physical stress: PF-4 ns changes *vs* baseline
Strike *et al*[101] 2006	Acute stress in male patients with survived ACS Cross sectional design 14 Emotion trigger group *vs* 20 non-trigger group		18 patients withdrawn medication *vs* 16 patients taking β-blockers, aspirin, statins, ACE inhibitors, no antidepressants	Stroop Colour Word Interference Test Speech task HADS Scale for MI-patients	Baseline imm post-stress task 30 min post stress 75 min post stress 120 min post-stress	PLA % Plt-mo agg % Plt-ne agg FACS	Emotion-trigger group: sig ↑all platelet outcome parameters (P < 0.001) in stress *vs* baseline *vs* non-emotion trigger group (P < 0.05), ↑Plt-mo agg at 30 min post stress (P < 0.05) in the emotion trigger group *vs* baseline *vs* non emotion trigger group
Strike *et al*[98] 2004	Acute stress in male CAD patients, stable disease and PCTA or coronary intervention Cross-sectional design 17 patients *vs* 22 healthy		Aspirin No statins 72 h No β-blockers 72 h	Stroop Colour Word interference task Mirror tracing task HADS Sleep quality assessed by Scale of Jenkins *et al*	Baseline Stress 30 min post-stress 75 min post-stress	% of PLA FACS	↑PLA (P < 0.05) in CAD at 75 min post stress *vs* healthy controls, group by trial interaction on PLA (P < 0.01)

Wallén *et al*[100] 1997	Acute mental and acute physical stress in patients with stable angina pectoris *vs* healthy controls Cross sectional design 113 patients (21 on aspirin) *vs* 50 matched controls		Aspirin, ACE inhibitors, digoxin, diuretics, β-blockers, calcium–channel blockers switched to study medication metoprolol and verapamil	Stroop Colour Word Conflict Test Ergometer examination	Baseline Stress-task	PF-4 β-TG ELISA	Physical exercise: patients ↑PF-4 ($P < 0.05$) and ↑β-TG ($P < 0.01$) *vs* baseline, healthy controls ↑β-TG ($P < 0.01$) and ↑PF-4 ($P < 0.01$) *vs* baseline; mental stress: ↑PF-4 ($P = 0.06$)[NS] and ↑β-TG ($P < 0.05$) in patients *vs* healthy controls
Tomoda *et al*[103] 1999	Acute mental stress in patients with essential hypertension Cross-sectional design 24 hypertensive (11 WHO stage Ⅰ, 13 WHO stage Ⅱ) patients *vs* 14 normotensive controls	WHO stage Ⅱ patients with proteinuria, elevated serum creatinin, left ventricular hypertrophy, hypertensive retinopathy	Not specified	10 min arithmetic test	Baseline Immediately post stress task	β-TG RIA	Stress induced increase β-TG ($P < 0.05$) in WHO stage Ⅰ and Ⅱ patients *vs* rest, baseline β-TG levels ($P < 0.05$) in WHO stage Ⅱ *vs* WHO stage Ⅰ *vs* controls

Plt: Platelet; %: Percentage of; P-sel: P-selectin; PF-4: Platelet factor 4; β-TG: β-thromboglobulin; FbR: Firbrinogen receptor binding; MNC: Mononuclear cell; CAD: Coronary artery disease; CHD: Coronary heart disease; MI: Myocardial infarction; PCI: Percutanuos coronary intervention; PCTA: Percutaneous coronary angiography; BDI: Beck Depression Inventory; STAEI: State-Trait Anger Expression Inventory; PSS: Perceived Stress Scale; HADS: Hospital Anxiety and Depression Scale; ACE: Antgiotensin converting enzyme; MI: Myocardial infarction; PLA: Platelet-leukocyte aggregates; Plt-mo agg: Platelet-monocyte aggregates; Plt-ne agg: Platelet-neutrophil aggregates; imm: Immediately; SSRI: Selective serotonin reuptake inhibitor; ELISA: Enzyme linkes immunosorbent assay; FACS: Fluorescence-activated cell sorting; NS: Not significant.

not evaluated in the post-stress recovery period. Strike *et al*[98] were able to show significantly increased PLA levels in CAD patients at 75 min post-stress. This indicates that CAD patients are prone to prolonged platelet activation following acute stress. Therefore, further investigations are warranted to evaluate post-stress platelet activation in CAD patients. One point raised by the authors is the small sample which did not represent the average age of CAD patients. Moreover, participants' subjective feelings of stress (task difficulty, controllability, task involvement) were evaluated[97-99,101]. Subjective stress ratings were shown to have a significant effect on study results[98]. The positive value of the study carried out by Strike *et al*[101] is the immediate evaluation of possible emotional trigger events following hospital admission. One limitation is the small sample size consisting of male Caucasians.

The effect of an acute mental stress task on platelet aggregability and platelet bioactivity was also assessed in patients with essential hypertension[103]. These patients were staged according to WHO criteria. All drugs affecting platelet function were discontinued 4 wk prior to testing. Patients with secondary hypertension, diabetes, or coronary artery disease, were not included. Medical conditions associated with the essential hypertension can be seen from Table 2. The stress task consisted of a 10-min mental arithmetic test[104]. Plasma β-TG levels were evaluated by RIA. Patients with WHO Stage Ⅱ hypertension showed significantly higher resting β-TG values compared to those with WHO Stage Ⅰ hypertension and normotensive controls. Following the acute mental stress task, plasma β-TG levels significantly increased in WHO Stage Ⅰ hypertensive patients. Stress-induced alterations in platelet function were significantly greater in this group compared to normotensive patients. In WHO Stage Ⅱ hypertensive patients the acute mental stress tasks led to a similar change in outcome parameters. A limiting factor is the small sample size, and the authors mention that FACS analysis should be used for further investigations.

PTSD

PTSD is defined as a disorder of the stress response system[105,106] that develops subsequent to stressful events[106]. The stress response system dysregulation is characterized by an HPA axis and sympathethic hyperdrive, and multiple neurotransmitter systems (e.g., serotonin) are supposed to be involved. It has been shown that PTSD patients have a multitude of somatic comorbidities with inflammatory or autoimmune background, namely metabolic syndrome, rheumatoid arthritis, thyroid disease and psoriasis[106]. Prospectively, PTSD has been associated with the development of cardiovascular disease 15 years after a traumatizing event[107]. Platelets might provide a useful tool in PTSD research

because of the impact of serotonergic parameters and monoamine oxidase activity, as well as possible changes in platelet bioactivity. Platelet monoamine oxidase is reported to be a vulnerability marker for various psychiatric disorders, personality traits, and behavioral problems[108]. It is known that MAO-B serves a common polymorphism in intron 13 in the form of a single base A or G change. Age, sex, ethnicity, and smoking have been shown to affect MAO-B activity in platelets[109-111].

Four investigations used the assessment of platelet serotonin (5-HT) content in patients with PTSD (Table 3). Platelet serotonin content was investigated as a marker of suicidal behavior in PTSD patients, non-PTSD patients, and healthy volunteers[112]. In another study, platelets were used as a peripheral marker for psychotic symptoms in PTSD[113]. Mück-Seler *et al*[114] assessed the 5-HT content in war veterans with PTSD and comorbid depression. In another investigation, Pivac *et al*[115] measured the platelet 5-HT content and platelet MAO activity in war veterans and prisoners of war with PTSD. In all of these investigations, 5-HT content and MAO activity were determined by spectrofluorimetric methods. No significant difference in serotonin content or MAO activity was seen between war veterans with or without PTSD and healthy controls. One investigation indicated that platelet serotonin concentration is significantly lower in suicidal PTSD patients and suicidal non-PTSD patients[112]. According to the presence of psychotic symptoms in PTSD patients, a significant increase in platelet serotonin content has been demonstrated[113]. A correlation between platelet serotonin content and the degree of loss of appetite was found. The highest serotonin concentration was found in the group of war veterans with depression and a severe loss of appetite, compared to depressed PTSD patients without appetite loss and controls[114]. A significant correlation between platelet serotonin content and psychotic symptoms was observed. These investigations provide robust data showing that platelet serotonin content is not a peripheral biomarker for PTSD but that it might serve as a marker for various psychopathological symptoms. Possible confounding factors (gender, dietary habits, seasonal variations) were taken into consideration. Kovacic *et al*[112] recruited a large sample to study suicidal behavior; however, the non-PTSD group was heterogeneous including patients with depression, psychosis, personality disorder and acute stress disorder. Pivac *et al*[113] conducted their study in a group of 138 war veterans, where the sample of psychotic PTSD patients, as well as the group of depressed non-PTSD patients was very small[114].

Vidović *et al*[116] evaluated platelet reactivity to various agonists, namely epinephrine (EPI) and ADP measuring the formation of PLAs (e.g., platelet-monocytes, platelet-lymphocytes, platelet-neutrophils) and the expression of P-selectin on platelet surface, as well as the percentage of P-selectin expressed in war veterans with PTSD (Table 3). The results showed that platelet reactivity to ADP was stronger in PTSD patients, which was indicated by increases in P-selectin surface expression, higher percentage of P-selectin expressed, and increased percentage of platelet-neutrophil aggregates. Another investigation by Vidović *et al*[117] in PTSD war veterans assessed PLA formation and CD63 expression on platelet surface. In addition, the amount of soluble p-selectin in sera was also determined. No difference in activation markers was observed between healthy civilians and PTSD war veterans. The authors discuss this in connection with the small sample size. Regarding PTSD patients as an example of chronic mental stress with an increased risk for a variety of somatic comorbidities, the evaluation of platelet activation by P-selectin expression and PLA formation provides a useful research tool.

Platelet MAO-B activity and MAO-B intron 13 polymorphism have been measured in war veterans with PTSD who were divided into subgroups with or without psychotic features[108] (Table 3). MAO-B activity was measured by spectrofluorimetry. Genotyping was done by Taqman-based allele-specific PCR assay[113]. The results revealed a significant effect of smoking and diagnosis, as well as a significant interaction between diagnosis and genotype and its effect on MAO-B activity. Significantly lower MAO-B activity has been found in smokers. Psychotic features seemed to be strongly associated with higher MAO-B activity. MAO-B intron polymorphism was relevant for a small group of non-smoking psychotic PTSD patients carrying the A-allele, who showed a stronger enzyme activity. Possible confounding factors were studied in a large male sample group who were divided into many sub-groups partly consisting of very few people. The war veterans were seen to have psychiatric comorbidities such as depression, alcoholism, and/or anxiety disorder which were previously described to possibly influence platelet parameters.

An investigation by Cicin-Sain *et al*[118] was conducted to evaluate the platelet 5HT content, 5HT-uptake, and MAO-B activity in patients with combat-related PTSD and other psychiatric comorbidities (depression, alcohol dependence, personality disorder, and psychosis) compared to healthy controls. Most participants were receiving treatment involving psychotropic medication such as benzodiazepine, antipsychotics, tricyclic antidepressants, and atypical antidepressants. None of them took MAO inhibitors. For the analysis, patients were divided into subgroups according to possible medication interference with the SERT (e.g., clomipramine, fluoxetine) and with MAO activity (e.g., antipsychotics, cyclic antidepressants). No significant difference was observed in serotonin content nor uptake in patients and controls except in the group of participants taking serotonin reuptake inhibitors. MAO-B enzyme velocity was significantly reduced in PTSD patients, notwithstanding their drug status or potentially interfering therapy.

IMPLICATIONS AND FURTHER DIRECTIONS

In healthy men compelling data show enhanced platelet

Table 3 Platelet serotonin content and MAO activity and platelet activation markers in PTSD in cross sectional investigations

Study	Participants	Assessment inventory	Comorbidities	Medication allowed	Platelet outcome parameters	Results
Vidović *et al*[116] 2011	Platelet reactivity in PTSD 15 PTSD veterans *vs* 12 healthy controls	Mini International Neuropsychiatric Interview CAPS HAMD HAMA		Benzodiazepins Atypical antipsychotics No antidepressants No NSAIDs No anti-hypertensives No statins	Platelet reactivity to agonists (EPI, ADP, combination) P-sel exp % of P-sel % of PLA % of P-mo agg % of P-ne agg % of P-ly agg FACS	PTSD patients ↑P-sel exp ($P = 0.003$), ↑% P-sel exp ($P = 0.006$), ↑% Plt-ne agg ($P < 0.001$) *vs* healthy controls
Kovacic *et al*[112] 2008	Platelets as a marker of suicidality in PTSD patients 73 suicidal and 47 non-suicidal PTSD patients *vs* 45 suicidal and 30 non suicidal non-PTSD patients. 147 healthy men	SCID CAPS HDRS HAMA PANSS	Non-PTSD group: depression, psychosis, acute stress disorder, personality Disorder	Drug free veterans Drug free non-PTSD patient group (drug-naïve or wash-out period of 2 wk or no SSRI for 6 wk)	5-HT content Spectrofluorometric assessment	↓5-HT ($P < 0.029$) suicidal PTSD *vs* non-suicidal PTSD, ↓5-HT ($P < 0.01$) suicidal PTSD *vs* healthy
Pivac *et al*[108] 2007	MAO-B activity and MAO intron 13 polymorphism in PTSD 28 PTSD patients with psychotic features *vs* 78 PTSD without psychotic features *vs* 41 veterans without PTSD *vs* 242 male healthy control	SCID CAPS PANSS HAMD	PTSD patients wit h comorbid depression Alcoholism Anxiety disorders Panick disorder	Drug-free	MAO-B activity Spectrofluorimetric assay Intron 13 polymorphism Taqman PCR	Non-Smokers: psychotic PTSD *vs* veterans ($P = 0.001$), *vs* healthy ($P = 0.006$) ↑MAO-B activity; non-psychotic PTSD *vs* veterans ($P = 0.046$) ↑MAO-B activity Smokers: psychotic PTSD *vs* veterans ($P = 0.002$), *vs* healthy ($P = 0.001$) ↑MAO-B activity
Vidović *et al*[117] 2007	Platelet activation markers in PTSD 20 PTSD war veterans *vs* 20 age comparable healthy civilians	CAPS Clinical Global Impressions Scale	Hypertension Hyperlipidaemia Diabetes	No psychopharmacotherapy	% PLA % Plt-mo agg % Plt-ne agg % Plt-ly agg FACS sP-sel ELISA	Platelet outcome parameters: ns changes
Pivac *et al*[113] 2006	Platelet serotonin in PTSD patients with psychotic features 67 veterans with PTSD *vs* 36 veterans without PTSD *vs* 35 veterans with psychotic PTSD	CAPS PANSS HAMD		Drug-free	5-HT contents Spectrofluorimetric assay	↑5-HT psychotic PTSD *vs* PTSD ($P = 0.019$), *vs* veterans ($P = 0.040$), *vs* controls ($P = 0.029$)
Mück-Seler *et al*[114] 2003	Platelet serotonin in PTSD with comorbid depression 48 PTSD veterans (31 depressed *vs* 16 non-depressed) *vs* 17 non PTSD war veterans (4 depressed *vs* 13 non-depressed)	CAPS HAS DTS MADRS	Headaches Back-pain Gastro-intestinal symptoms	Drug-free for 2 wk	5-HT content Spectrofluorimetric assay	5-HT contents PTSD *vs* non PTSD *vs* healthy controls ($P = 0.11$)[NS] changes; ↑5-HT depressed veterans with severe appetite loss ($P < 0.05$) *vs* depressed PTSD without appetite loss *vs* controls
Pivac *et al*[115] 2002	Platelet 5-HT and MAO activity in PTSD 31 war veterans with PTSD *vs* 22 war veterans without PTSD *vs* 22 prisoners of war with PTSD	MADRS CAPS	No alcohol or drug abuse 1 mo prior	Drug-free	5-HT content MAO-activity Spectrofluorimetric method	5-HT ($P = 0.31$)[NS]; MAO activity ($P = 0.12$)[NS]; No correlation to rating scales

Cicin-Sain *et al*[118] 2000	5-HT level, kinetics of serotonin transporter, MAO activity 63 PTSD patients *vs* 43 healthy controls	Watsons PTSD questionnaire	PTSD patients comorbid depression, alcohol dependence, personality disorder, psychosis	Benzodiazepines, neuroleptics, TCAs, SSRIs, atypical anti-depressants	5-HT content 5-HT uptake MAO-B activity Spectrofluorimetric Radioisotypic method	5-HT^{NS}; Serotonin transporter kinetics^{NS}, ↓MAO-B velocity ($P < 0.05$) in patients *vs* healthy controls

PTSD: Posttraumatic stress disorder; 5-HT: Serotonin; MAO: Monoamine oxidase; EPI: Epinephrine; ADP: Adenosine-di-phosphat; SCID: Structured clinical interview; CAPS: Clinician Administred PTSD Scale; HDRS: Hamiton Depression Rating Scale; HAMA: Hamilton anxiety rating scale; PANSS: Positive and negative syndrom scale; MADRS: Montgomery asperg depression scale; HAMD: Hamilton rating scale for depression; HAS: Hamilton anxiety scale; DTS: Davidson trauma scale; %: Percentage of; PLA: Platelet-leukocyte aggregates; Plt-mo agg: Platelet-Monocyte aggregates; Plt-ne agg: Platelet-neutrophil aggregates; P-ly agg: Platelet-lymphocyte aggregates; P-sel: P-selectin; sPsel: Soluble P-selectin; exp: Expression; TCA: Tricyclic antidepressants; SSRI: Selective serotonin reuptake inhibitor; NSAID: Non steroidal anti inflammatory durg; FACS: Fluorescence-activated cell sorting; NS: Not significant.

activity due to mental stress. Further research should focus on the post-stress recovery period; in addition, replication of present results is warranted[88]. Platelet activation in women needs to be studied more intensively in light of a possible influence of female hormones. In this context it must be mentioned that platelet investigations should accurately control for cofounding lifestyle, dietary habits, and medication. Socioeconomic status and personal feelings of stress should also be taken into account[88,98].

With regard to an elderly population (mean age 70), strong data have been collected that provide an excellent explanatory model for the study of the interaction of acute and chronic mental stress conditions, mood symptoms, and platelet activation. As depressive and anxious symptoms were predictive for p-selectin reactivity, future investigations should take into consideration the interaction of stress-induced mood symptoms and platelet activation.

In cardiovascular disease, mental stress revealed consistently elevated PLA levels[98,99,101], but platelet activation in the post-stress period needs further research. These findings indicate that adequate psychosocial stress management might be of clinical relevance for this patient group[119]. Data on platelet stress reactivity in females and various ethnic groups with cardiovascular disease are missing.

The assessment of circulating platelet activation compounds in sera or plasma provides conflicting results. This observation is in line with results collected under physical stress conditions[120-125] and in depression[126-129]. Thus, the evaluation of platelet activation markers by FACS, and especially the determination of PLA levels, has been suggested to be the most sensitive technique[83].

The evaluation of serotonin content and MAO activity in the platelets of PTSD patients might provide a useful tool for the assessment of various psychopathological symptoms. These show an association between serotonin content and appetite loss in depressed patients, suicidality, and psychotic features[112-114], but not an association with the diagnosis itself. According to previous research data, the present studies strictly checked for possible cofounding variables (smoking habits, seasonal variations, gender, and medication). The possible role of platelet serotonergic parameters as peripheral biomarkers has been controversially discussed in the past[130,131].

Although the results of PLA in PTSD patients carried out by FACS are promising, further research is warranted in larger sample sizes. This analysis may offer the possibility to further investigate the association between PTSD and a variety of cardiovascular and autoimmune diseases.

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