Platelets, inflammation and anti-inflammatory drugs in ACS and CAD
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Introduction

In this theme issue, which is based on the annual meeting of the European Platelet Academy (EPA) 2014 in Dresden, Germany (organiser: K. Schrörr), the authors aimed to present and discuss newest developments in an important topic, exciting also for its clinical relevance: The relationship between platelets, inflammation and anti-inflammatory agents. In the following paragraphs representing important subtopics we summarise recent knowledge.

Platelets as inflammatory cells

Platelet reactivity in patients with acute coronary syndromes (ACS) but also stable coronary heart disease (CAD) is usually understood as enhanced stimulated aggregation response ex vivo (1–3). However, aggregate formation is not the only and, probably, also not the most important function of platelets. These “cells” not only form aggregates via initial spreading and secretion of storage products, they also are a rich source of numerous chemical factors. These factors mediate aggregate and clot formation with incorporation of white cells and fibrin formation. Thus, platelets are storage site and source of potent autocrine and paracrine factors that stimulate thrombotic, inflammatory and immune responses (4, 5). Consequently, they have been considered inflammatory cells which interface thrombosis with inflammation (6, 7). An important manuscript by Thomas and Storey in this Theme Issue summarises the current knowledge about platelets in inflammation (8). In this context, it should also be considered that not all platelets may be the same with respect to their functional activity. Platelet turnover, as seen from an enhanced fraction of young, reticulated platelets, which are functionally more active and are an important variable for overall platelet reactivity, in particular in patients with acute and chronic cardiovascular disorders (9). The clinical significance of these complex interactions between platelet-derived mediators and other cells, i.e. so-called “heterotypic” platelet function aggregation or release in response to appropriate stimuli or indirect stimulation of other cells in the vicinity by cell/cell interactions.

Platelet-derived inflammatory mediators

Where do these mediators come from? First, platelet dense and alpha granules contain a plethora of vasoactive, inflammatory and immunoreactive mediators, including P-selectin (CD 62), CD40L, transforming growth factor (TGF)-β, several growth factors, serotonin and others. In addition they can generate mediators, such as thromboxane A2 “on request”. Second, platelets will stimulate other cells in the vicinity to generate or release mediators after initial stimulation. For example, platelet expression of platelet P-selectin mediates the formation of platelet-leukocyte aggregates and upregulates leukocyte release of pro-inflammatory cytokines interleukin (IL)-1β, IL-8, tumour necrosis factor (TNF)α and monocyte chemotactic protein (MCP)-1 as well as expression of adhesion molecules.

Elevated levels of circulating platelet-leukocyte aggregates are also found in patients suffering from the prothrombotic and inflammatory conditions of atherosclerosis, a continuous low-grade inflammatory state. Stable CAD in these patients is associated with increased levels of C-reactive protein (CRP), fibrinogen, IL-6, macrophage migration inhibitory factor, RANTES and others. In a large population-based study of stable CAD patients it was found that high hsCRP levels correlated positively with increased platelet count, immature platelet count, and thrombopoietin levels (12). All of these have been associated with increased risk of cardiovascular events in CAD patients and some of them with enhanced platelet activation and aggregation. However, CRP and other inflammatory markers provide only limited additional predictive value to classical risk factors such as smoking, blood pressure, and cholesterol levels (13). Nevertheless, there is evidence for a bifunctional involvement of platelets in these processes: direct generation or release in response to appropriate stimuli or indirect stimulation of other cells in the vicinity by cell/cell interactions.
Antiplatelet drugs and their anti-inflammatory capacity

Since platelets stimulate prothrombotic and proinflammatory events inside the circulation, probably in tight association with the vessel wall, the question arises whether these effects are also sensitive to antiplatelet agents. It is to be expected that antiplatelet drugs should also have anti-inflammatory actions, directly or indirectly platelet-mediated effects which should contribute to their efficacy in clinical use.

Aspirin

Aspirin was the first established antiplatelet compound and is still “gold standard” for antiplatelet treatment, either as monotherapy or a part of dual antiplatelet therapy (DAPT) (13). Several aspirin-sensitive markers of inflammation, such as CRP, leukocyte numbers or fibrinogen as well as inflammatory cytokines, such as IL-6 and “macrophage colony stimulating factor” (MCSF) are elevated in patients with chronic stable angina and ACS and are significantly reduced by aspirin at antiplatelet doses (14).

The primary pharmacological target of aspirin is platelet-COX-1-dependent formation of thromboxane A2 (TXA2), the only significant COX-product of platelets, with both autocrine and paracrine functions. It is not entirely clear, whether the interaction of aspirin with inflammatory mediators is a direct, TXA2-mediated effect or indirectly mediated via the antiplatelet activity (15). Interestingly, aspirin in contrast to ADP antagonists was found also to inhibit (retard) clotting associated thrombin formation ex vivo (16) and has also been found to act synergistically in this respect with low-dose rivaroxaban in an experimental setting (17). Clopidogrel (on top of aspirin) in DAPT was also found to inhibit thrombin-induced platelet-fibrin clot formation (18). This suggests that aspirin-induced inhibition of thrombin formation is consequence of its antiplatelet effect, since this action is lost in case of aspirin “resistance” (19) and probably an important component of the anti-thrombotic/anti-inflammatory action of aspirin in ACS.

In endothelial and epithelial cells acetylation of COX-2 by aspirin alters the enzyme activity into a 15-lipoxygenase which can generate “aspirin-triggered lipoxin” (ATL) bei interaction with white cell lipoxygenases. Lipoxins are antiinflammatory and inflammatin resolving compounds. This action is unique to aspirin and not shared with any NSAID, coxib or ADP-P2Y12 antagonist. Inhibition of thromboxane formation by antiplatelet doses of 75 mg aspirin/day has been shown to inhibit leukocyte accumulation at local inflammatory sites and to stimulate the production and action ATL in man (20). ATL formation requires that platelets interact directly with adherent neutrophils/monocytes, as because it only occurs after platelet activation. Considering all these dose-dependent effects of aspirin in different cell types, one can conclude that its anti-inflammatory impact is a combination of both, its influence on platelet- and leukocyte-mediated inflammatory responses.

ADP-P2Y12 receptor inhibitors

ADP-P2Y12 receptor inhibitors also reduce platelet release of pro-inflammatory α-granule contents and the formation of pro-inflammatory platelet-leukocyte aggregates. Recent studies show that the P2Y12 receptor is expressed not only in platelets but also in other cell types, such as monocytes, vascular smooth muscle cells, dendritic cells and lymphocytes. Therefore effects of ADP-antagonists are not only expected in platelets but also in the target cells mentioned above (21). The P2Y12 ADP receptor has also been linked to other processes, including fibrinogen receptor activation and CD62P exposure.

By inhibiting platelet reactivity to ADP and a broad range of other agonists, clopidogrel (active metabolite) has been shown to inhibit the release of pro-inflammatory mediators from platelet α-granules ex vivo. In patients with ACS, it has been shown that soluble P-selectin and CD40L levels decrease after a loading dose of clopidogrel. However, clopidogrel monotherapy did not appear to change levels of soluble P-selectin, sCD40L, transforming growth factor (TGF)-β or MCP-1 compared to aspirin monotherapy in stable coronary artery disease patients in the ASCET study (22). In addition platelet-mediated immune responses have implications for the progression of cardiovascular diseases and also other inflammatory diseases of several organs. Both aspirin and P2Y12 inhibitors attenuate platelet-leukocyte interactions, thereby also modulating chronic inflammatory and immune responses. However, the balance of evidence does not suggest additional anti-inflammatory effects of clopidogrel monotherapy compared to aspirin monotherapy (23). There is also limited evidence that clopidogrel may have off-target effects on inflammation that are not mediated by P2Y12.

Prasugrel

Prasugrel (active metabolite) more potently inhibits ADP-induced platelet P-selectin expression and platelet-leukocyte aggregate formation. Inhibition of platelet-neutrophil aggregate formation by prasugrel active metabolite has been shown to decrease neutrophil activation, as demonstrated by lower expression of Mac-1 (24). Prasugrel has a greater inhibitory effect on platelet CD40L and P-selectin expression than clopidogrel in patients undergoing PCI. Prasugrel, in addition to aspirin, reduces ADP-induced platelet P-selectin and platelet-monocyte aggregate formation compared to clopidogrel in addition to aspirin in patients with stable coronary artery disease (25). It remains to be established whether this has an additional anti-inflammatory effect.

Ticagrelor

Ticagrelor is another platelet P2Y12 receptor antagonist. In contrast to clopidogrel and prasugrel, the action of ticagrelor is reversible and the compound is not irreversibly fixed to the platelet receptor. Ticagrelor in addition inhibits cellular uptake of adenosine by inhibiting the equilibrative nucleoside transporter-1 (ENT1). Regarding inflammation, ticagrelor was unexpectedly associated with fewer pulmonary infections and deaths related to infection than clopidogrel. Also, surprisingly, ticagrelor was associated with slightly higher levels of IL-6 and CRP at discharge than...
clopigrel in PLATO. This demonstrates a differential effect of the medications on inflammatory responses. Ticagrelor has now also been shown to increase extracellular levels of adenosine in patients with ACS. This appears to have clinically relevant effects, since ticagrelor potentiates adenosine induced coronary vasodilation and dyspnoea. Adenosine is a major modulator of inflammation and innate immune responses. However, adenosine-mediated effects of ticagrelor are complex. At low concentrations, adenosine predominantly acts on high affinity leukocyte A1 receptors. This has mostly pro-inflammatory effects, including potentiation of neutrophil chemotaxis and phagocytosis and macrophage phagocytosis. At higher concentrations, adenosine predominantly acts on lower affinity leukocyte A2A and A2B receptors. This has mostly anti-inflammatory. Thus, ticagrelor due to its dual inhibition of platelet P2Y12 receptors and ENT1 may be pro-inflammatory or anti-inflammatory, depending on the context (23).

A review by Schrottmaier et al. in this Theme Issue aims to summarise the current knowledge on platelet-leukocyte interactions and the impact of aspirin and P2Y12-inhibition on platelet-mediated immune responses in various diseases (21). Finally, an overview by Müller et al. about antiinflammatory effects of antiplatelet drugs in acute coronary syndromes and coronary artery disease (26) as well as one by Larsen et al. (27) on the influence of low-grade inflammation on platelets in patients with stable coronary artery disease complete this Theme Issue.

Summary

Taken together, current evidence suggests that conventional antiplatelet drugs, such as aspirin, clopidogrel, prasugrel and ticagrelor also have antiinflammatory actions in different experimental settings and clinical conditions. These actions are thought to be primarily related to their antiplatelet effect. While there is significant evidence for aspirin-related antiinflammatory platelet actions, the situation with ADP-antagonists is less clear, as it has been reported (28) that treatment with ticagrelor and clopidogrel did not lead to significant differences regarding the inflammatory biomarkers CRP, IL-6, and sCD40L in patients with NSTE-ACS among treatment groups at baseline, discharge, and at four weeks (23). However, these actions will be seen during DAPT and likely the anti-aggregatory effect might also be stronger with combined use.

Conflicts of interest

None declared.

References