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Aspirin and lipid mediators in the cardiovascular system

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ABSTRACT

Aspirin is an unique compound because it bears two active moieties within one and the same molecule: a reactive acetyl group and the salicylate metabolite. Salicylate has some effects similar to aspirin, however only at higher concentrations, usually in the millimolar range, which are not obtained at conventional antiplatelet aspirin doses of 100–300 mg/day. Pharmacological actions of aspirin in the cardiovascular system at these doses are largely if not entirely due to target structure acetylation. Several classes of lipid mediators become affected: Best known is the cyclooxygenase-1 (COX-1) in platelets with subsequent inhibition of thromboxane and, possibly, thrombin formation. By this action, aspirin also inhibits paracrine thromboxane functions on other lipid mediators, such as the plateletstorage product sphingosine-1-phosphate (S1P), an inflammatory mediator. Acetylation of COX-2 allows for generation of 15-(R)HETE and subsequent formation of "aspirin-triggered lipoxin" (ATL) by interaction with white cell lipoxygenases. In the cardiovascular system, aspirin also acetylates eNOS with subsequent upregulation of NO formation and enhanced expression of the antioxidans heme-oxygenase-1. This action is possibly also COX-2/ATLmediated. Many more acetylation targets have been identified in live cells by quantitative acid-cleavable activity-based protein profiling and might result in discovery of even more aspirin targets in the near future.

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1. Introduction—fresh insights into the pharmacology of aspirin

When aspirin was introduced into the clinics at the beginning of last century, it was generally believed that the compound itself was only the prodrug of its active metabolite salicylate and, needs first to become hydrolized in order to release the active salicylate moiety from the inactive "precursor" (Fig. 1). Consequently, it was assumed that the salicylate moiety fully accounts for all of the pharmacological actions of aspirin [1]. This view has changed fundamentally after detection of inhibition of prostaglandin formation by aspirin by Sir John Vane [2] and, shortly after, the acetylation of the platelet cyclooxygenase (COX) as the molecular target of aspirinís antiplatelet effect [3]. Clearly, part or even the majority of the analgesic/anti-inflammatory actions of aspirin in the early days of its use at doses of several grams per day was due to the salicylate component, specifically all of the toxicity—in 1918 the JAMA recommended 1.0–1.3 g every 1–3 h for treatment of flu symptoms [4]. However, it is now clear that apparently all of the clinically relevant aspirin actions in the cardiovascular system can be obtained at much smaller doses and - importantly - are mostly if not entirely due to target-specific acetylation. Most relevant is the acetylation of serine$_{530}$ in the platelet COX-1, resulting in reduced generation of thromboxane A_2. Actually, more than 500 target proteins of aspirin induced acetylation have been identified by quantitative acid-cleavable activity-based protein profiling [5] and there is recent evidence also for acetylation of a number of transcription factors as well as RNA, DNA and low-molecular weight metabolites, such as coenzyme A [6]. Thus, not all effects of aspirin in the cardiovascular system may be lipid-related and there is cleary a large field of future research.

Another class of pharmacological effects of aspirin on lipid mediators in the cardiovascular system results from the modulation rather than inhibition of the inducible form of cyclooxygenase, COX-2. A most challenging finding in this respect was the detection that in COX-2, in contrast to COX-1, acetylation does not result in inhibition but rather modulation of its enzymatic activity, resulting in the generation of a new product, 15-(R)-HETE. 15-(R)-HETE then can interact with lipoxygenase(s) of white cells to generate "aspirin-triggered lipoxin" (ATL) which like other lipoxins, is an anti-inflammatory mediator. The ATL-lipoxin axis also might stimulate NO-synthase in platelets and endothelial cells and upregulate heme oxygenase-1 (HO-1), an antioxidative enzyme [7,8].

This paper reviews the evidence for aspirin effects on these lipid mediators in the cardiovascular system. In focus as primary pharmacological candidate targets are the cyclooxygenases COX-1 and COX-2. The hypothesis is put forward that all of the effects of aspirin in the cardiovascular system that are seen at commonly recommended antiplatelet doses: 75–325 mg/day in the US [9] or 75–150 mg in Europe [10] after initial loading with 250–500 mg intravenously (i.v.) or up to 1 g/day for pain relief are solely due to target protein acetylation without any evidence for direct involvement of salicylate.

2. Inhibition of cyclooxygenase-1 (COX-1) by aspirin—the dose issue and pharmacokinetic aspects

The first pharmacological issue to be clarified before discussing specific effects of aspirin on lipid mediators, is (i) which local levels of aspirin and salicylate are required to inhibit COX-1 and COX-2 with the downstream mediators thromboxane, prostaglandins, lipoxins and nitric oxide and (ii) whether these concentrations can also be obtained with conventional doses in vivo. In the human, antiplatelet doses of aspirin, i.e. 75–325 mg/day result in peak plasma acetylsalicylate levels of 1–3 μg/ml and about 10–12 μg/ml at the 1 g analgesic dose [11,12]. Because of the longer half-life, concentrations of the salicylate metabolite in plasma are about 4–8 fold higher. The maximum is below the millimolar level which is used in most in vitro studies (in aqueous media!) [13]. These salicylate concentrations, frequently above 5–10 mM completely uncouple oxidative phosphorylation with numerous subsequent effects, for example non-specific kinase inhibition [14]. Thus, it is likely that all biologically relevant effects of aspirin on COX-1 and COX-2 in the cardiovascular system at antiplatelet doses are largely if not entirely acetylation-mediated. Of course, all of these doses and concentrations, respectively, of aspirin are fully sufficient to completely prevent any platelet-COX-1-dependent thromboxane formation [12,15–17].

In this context, the so-called aspirin "resistance" or "high on aspirin treatment platelet reactivity" (HATPR), i.e. a reduced antiplatelet action of the compound, should be mentioned HATPR is a controversial issue. Part of the controversy might be due to different definitions [18]. While a pharmacological failure of aspirin to block platelet COX-1 is very random (≤2%) – in the absence of negative interaction with other COX-(1) inhibitors –, a clinical HATPR, i.e. treatment failure, is more frequent. It is in the range of 20–30% and significantly influenced by the method of its determination [19].

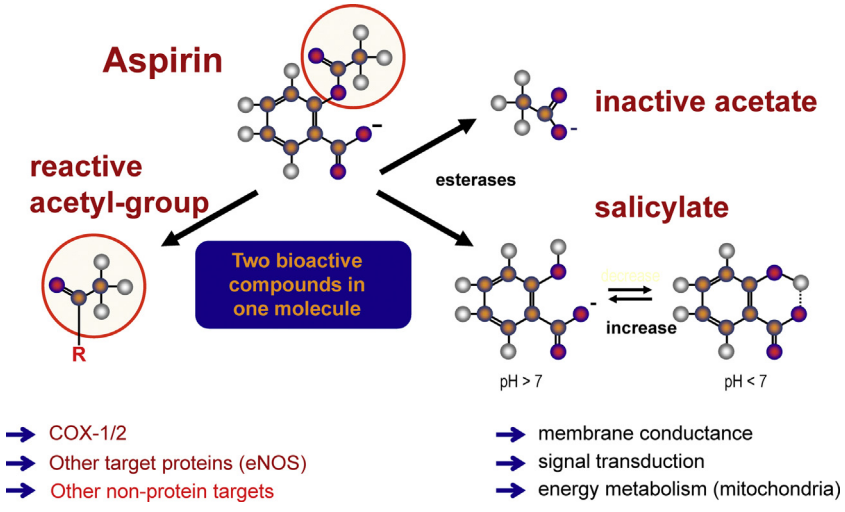

Fig. 1. The two active principles in aspirin – reactive actetyl- and salicylate – and selected protein targets (©Dr. Schrör Verlag, 2015).