LXIII JCET LECTURE, 22.05.2015, 9.00

Aspirin, the cardiovascular system and cancer – the 2015 view

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Aspirin is an unique compound: It bears two active moieties within one and the same molecule: A reactive acetyl group and the salicylate metabolite. Pharmacological actions of aspirin in the cardiovascular system are caused by target structure acetylation. Several classes of 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 platelet-derived mediators, such as the platelet-storage product sphingosine-1-phosphate (S1P), an inflammatory mediator. “High on aspirin treatment platelet reactivity” (“resistance”) does exist but is no pharmacological failure of the drug to act but rather due to pharmacokinetic and pharmacodynamic interactions. The clinical efficacy of aspirin in secondary prevention of myocardial infarction and stroke is well documented, a new attractive issue is prevention of venous thromboembolism. Aspirin at antiplatelet doses also might prevent colorectal cancer and prolong survival (distal metastases) in selected populations. Retrospective analyses of randomized cardiovascular prevention trials suggest an about 20% protection rate. The mode of action is speculative but should be working at antiplatelet doses, i.e. acetylsalicylate plasma levels of < 10 µM. We hypothesize a connection to the antiplatelet effect, i.e. inhibition of secretion of platelet-derived inflammatory mediators, such as S1P. 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. Possibly aided by the introduction of the new micronized aspirin formulation with significantly higher acetylation potential in the systemic circulation.

CURRICULUM VITAE

Education:

1961 - 1967 Medicine, Universität Halle/Wittenberg

1967 - 1972 Pharmacology, Universität Halle/Wittenberg

External residencies:

Wellcome Research Laboratories (UK); Supervisor: Sir John R. Vane, Department of Physiology, Jefferson Medical College, Philadelphia (USA); Supervisor: Prof. A.M. Lefer, Visiting Professor Medical University of South Carolina at Charleston (USA) (Prof. P.V. Halushka), Visiting Professor Department of Internal Medicine, Division of Hematology, University of Texas Medical Center, Houston (USA) (Prof. K.K. Wu)

Positions held:

1967 - 1978 Research Assistant, Departments of Pharmacology, Universities Halle/Wittenberg, Mainz, Köln

1979 - 1984 Assistant Professor, Department of Pharmacology, University Köln

1984 - 1986 Associate Professor, Department of Pharmacology, University Köln

1986 - 2010 Professor of Pharmacology and Chairman of the Department of Pharmacology and Clinical Pharmacology, Heinrich-Heine-University Düsseldorf

2003 - 2006 Chairman of the Board, Working Group of the Chairmen of Departments of Pharmacology, Clinical Pharmacology and Toxicology at German Speaking Universities

2005/2010 Chairman of the German Society for Pharmacology

2007 - 2010 President of the German Society for Experimental and Clinical Pharmacology & Toxicology (DGPT)

since 2012 Chairman of the European Platelet Academy, member since 2007

1992 Member of the Deutsche Akademie der Naturforscher Leopoldina (National Academy of Sciences)

2012 Schmiedeberg-Lifetime-Achievement-Award of the Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie for Excellence in Science

Hungarian Society for Experimental and Clinical Pharmacology (Honorary Member)

National Health Research Institutes, Taiwan (Scientific Advisory Board Member)

Publications:

About 500 original publications, reviews and several books on physiological and pharmacological aspects of myocardial infarction, pharmacology of platelet function, blood coagulation, prostaglandins, cellular effects of coagulation factors (thrombin, Xa) and signal transduction in vascular smooth muscle cells. Pharmacology and Clinics of Aspirin

Selected Publications:

Schrör K, Darius H, Matzky R, Ohlendorf R: The antiplatelet and cardiovascular actions of a new carbacyclin derivative (ZK 36374) - equipotent to PGI2 in vitro. Naunyn-Schmiedeberg's Arch Pharmacol 316: 252-256 (1981) (first report on pharmacology of iloprost)

Schrör K, Ohlendorf R, Darius H: Beneficial effects of a new carbacyclin derivative - ZK 36374 - in acute myocardial ischemia. J Pharmacol Exp Ther 219: 243-249 (1981) (first report on cardioprotective actions of iloprost in vivo)

Schrör K, Köhler P, Müller M, Peskar BA, Rösen P: Prostacyclin-thromboxane interactions in the platelet-perfused in vitro heart. Am J Physiol 241: H18-H25 (1981) (Description of a new in vitro model to study platelet vessel interaction in an intact organ circulation)

Schrör K, Addicks K, Darius H, Ohlendorf R, Rösen P: PGI2 inhibits ischemia-induced platelet activation and prevents myocardial damage by inhibition of catecholamine release from adrenergic nerve terminals. Evidence for cyclic AMP as a common denominator. Thromb Res 21: 175-180 (1981) (first description of an antiadrenergic action of prostacyclins)

Schrör K, Löbel P, Steinhagen-Thiessen E: Simvastatin reduces platelet thromboxane formation and restores normal platelet sensitivity against prostacyclin in type IIa hypercholesterolemia. Eicosanoids 2: 39-45 (1989) (first description of an antiplatelet effect of statins and its molecular mode of action)

Woditsch I, Schrör K: Prostacyclin rather than endogenous nitric oxide is a tissue protective factor in myocardial ischemia. Am J Physiol 263: H1390-H1396 (1992)

Schröder H, Schrör K: Prostacyclin-dependent cyclic AMP formation in endothelial cells. Naunyn Schmiedeberg's Arch Pharmacol 347: 101-104 (1993) (first description of endogenous regulation of PGI2-receptors via cAMP)

Woditsch I, Schrör K: Reduced endothelium-dependent relaxation at enhanced NO release in hearts of hypercholesterolemic rabbits. Br J Pharmacol 111: 1035-1040 (1994) (first description of a functionally active iNOS – which was not known at the time)

Bracht F, Schrör K: Isolation and identification of aptamers from defibrotide that act as thrombin antagonists in vitro. Biochem Biophys Res Comm 200: 933-937 (1994) (aptameric structures were patented (before publication)

Hohlfeld T, Zucker T-P, Meyer J, Schrör K: Expression, function and regulation of E-type prostaglandin receptors (EP_3) in the nonischemic pig heart. Circ Res 81: 765-773 (1997) (first evidence for EP3 as the cardiac target of prostacyclin)

Zucker T-P, Bönisch D, Muck S, Weber A-A, Bretschneider E, Glusa E, Schrör K: Thrombin-induced mitogenesis in coronary artery smooth muscle cells is potentiated by thromboxane A_2 and involves upregulation of thromboxane receptor mRNA. Circulation 97:589-595 (1998)

Zimmermann KC, Sarbia M, Schrör K, Weber, A-A: Constitutive cyclooxygenase-2 expression in healthy human and rabbit gastric mucosa. Mol Pharmacol 54: 536-540 (1998) (first description of COX-2 in the stomach wall mucosa)

Weber A-A, Zimmermann KC, Meyer-Kirchrath J, Schrör K: Cyclooxygenase-2 in human platelets as a possible factor in aspirin resistance. Lancet 353: 900 (1999) (first description of COX-2 in human platelets)

Zimmermann KC, Sarbia M, Weber AA, Borchard F, Gabbert HE, Schrör K: Cyclooxygenase-2 expression in human esophageal carcinoma. Cancer Res 198-204 (1999) (until now about 850 citations!)

Bretschneider E, Braun M, Fischer A, Wittpoth M, Glusa E, Schrör K: Factor Xa acts as a PDGF-independent mitogen in human vascular smooth muscle cells. Thromb Haemost 84: 499-505 (2000) (description of a PDGF-independent mode of mitogenesis by clotting factors)

Bretschneider E, Kaufmann R, Braun M, Nowak G, Glusa E, Schrör K: Evidence for functionally active protease-activated receptor-4 (PAR-4) in human vascular smooth muscle cells. Br J Pharmacol 132: 1441-1446 (2001) (first description of a functionally active PAR-4 in human SMC)

Weber A-A, Hermann A, Rauch BH, Schrör K: Molecular identity of platelet CD40 ligand (CD40L). Thromb Haemost 86: 718 (2001)

Weber A-A, Schrör K: Differential inhibition of adenosine diphosphate- versus thrombin receptor-activating peptide-stimulated platelet fibrinogen binding by abciximab due to different glycoprotein IIb/IIIa activation kinetics. Blood 98: 1619-1621 (2001)

Weber A-A, Przytulski B, Schanz A, Hohlfeld T, Schrör K: Towards a definition of aspirin resistance: a typological approach. Platelets 13: 37-40 (2002) (Definition of aspirin resistance in pharmacological terms)

Rauch BH, Bretschneider E, Braun M, Schrör K: Factor Xa releases matrix metalloproteinase-2 (MMP-2) from human vascular smooth muscle cells and stimulates the conversion of pro-MMP-2 to MMP-2. Role of MMP-2 in factor Xa-induced DNA synthesis and matrix invasion. Circ Res 90: 1122-1127 (2002)

Schrör K, Zhu Y, Saunders MA, Deng W-G, Xu X-M, Meyer-Kirchrath J, Wu KK: Obligatory role of cyclic adenosine monophosphate response element in cyclooxygenase-2 promoter induction and feedback regulation by inflammatory mediators. Circulation 105: 2760-2765 (2002) (evidence for cAMP-feedback regulation of COX-2)

Zimmermann N, Wenk A, Kim U, Kienzle P, Weber A-A, Gams E, Schrör K, Hohlfeld T: Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. Circulation 108: 542-547 (2003)

Bretschneider E, Spanbroek R, Lötzer K, Habenicht AJR, Schrör K: Evidence for functionally active protease-activated receptor-3 (PAR-3) in human vascular smooth muscle cells. Thromb Haemost 90: 704-709 (2003) (first description of a functionally active PAR-3 in human SMC)

Stampfuss JJ, Schrör K, Weber A-A: Inhibition of platelet thromboxane receptor function by a thrombin-receptor pepducin. Nature Med 9: 1447-1448 (correspondence) (2003)

Censarek P, Freidel K, Udelhoven M, Ku S-J, Hohlfeld T, Meyer-Kirchrath J, Schrör K, Weber A-A: Cyclooxygenase COX-2a, a novel COX-2 mRNA variant, in platelets from patients after coronary artery bypass grafting. Thromb Haemost 92: 925-928 (2004) (dection of a new splice variant of COX-2 which is probably functionally inactive)

Rabausch K, Bretschneider E, Sarbia M, Meyer-Kirchrath J, Censarek P, Pape R, Fischer JW, Schrör K, Weber A-A: Regulation of thrombomodulin expression in human vascular smooth muscle cells by COX-2-derived prostaglandins. Circ Res 96: e1-e6 (2005)

Martin M, Meyer-Kirchrath J, Kaber G, Jacoby C, Flögel U, Schrader J, Rüther U, Schrör K, Hohlfeld T: Cardiospecific overexpression of the prostaglandin EP_3 receptor attenuates ischemia-induced myocardial injury. Circulation 112: 400-406 (2005) (evidence that EP3 upregulation is the target of cardioprotective prostaglandins)

Bretschneider E, Uzonyi B, Weber A-A, Fischer JW, Pape R, Lötzer K, Schrör K: Human vascular smooth muscle cells express functionally active endothelial cell protein C receptor. Circ Res 100: 255-262 (2007 (first description of a regulated EPRC as thrombin/thrombomodulin target in human SMC)

Pape R, Rauch BH, Rosenkranz AC, Kaber G, Schrör K: Transcriptional inhibition of protease-activated receptor-1 expression by prostacyclin in human vascular smooth muscle cells. Arterioascler Thromb Vasc Biol 28:534-40 (2007 (first evidence of transcriptional regulation of PAR by cAMP elevation)

Schrör, K., Bretschneider E, Fischer K, Fischer JW, Pape R, Rauch BH, Rosenkranz AC, Weber AA: Thrombin receptors in vascular smooth muscle cells – function and regulation by vasodilatory prostaglandins. Thromb Haemost 2103, 884-90 (2010)

Rauch, BH, Rosenkranz, AC, Ermler S, Böhm A, Driessen J, Fischer JW, Sugidachi A, Jakubowski JA, Schrör K: Regulation of functionally active P2Y12 receptors by thrombin in human smooth muscle cells and the presence of P2Y12 in carotid artery lesions. Arterioscler Thromb Vasc Biol 30: 2434-42 (2010) (first presentation of a thrombin-regulated and functionally active P2Y12 receptor in SMC)

Schrör K, Huber K, Hohlfeld T: Functional testing methods for the antiplatelet effects of aspirin. Biomarkers Med 5:31-42 (2011)

Rosenkranz AC, Rauch BH, Doller A, Eberhardt W, Böhm A, Bretschneider E, Schrör K: Regulation of human vascular protease-activated receptor-3 through mRNA stabilization and the transcription factor nuclear fator of activated T cells (NFAT). Mol Pharmacol 80:337-344 (2011) (First description of NFAT as mediator of cAMP induced regulator of PAR-expression)

Schrör K: Pharmacology and cellular/molecular mode of action of aspirin and non-aspirin NSAIDs in colorectal cancer. Best Pract Res Clin Gastroenterol 25:473-484 (2011)

Hohlfeld, T., Saxena A, Schrör K: High on treatment platelet reactivity against aspirin by non-steroidal anti-inflammatory drugs –pharmacological mechanisms and clinical relevance. Thromb Haemostas 109: 3825-33 (2013)

Polzin A, Zeus T, Schrör K, Kelm M, Hohlfeld T: Dipyrone (metamizole) can nullify the antiplatelet effect of aspirin in patients with coronary artery diseaase. JACC 62:1725-6 (2013)

Mahajan-Thakur S, Sostmann BD, Fender AC, Behrendt D, Felix SB, Schrör K, Rauch B: Sphingosine-1-phosphate induces thrombin receptor PAR-4 expression to enhance cell migration and COX-2 formation in human monocytes. J Leukocyte Biol 96:611-18 (2014)

Pavic G, Grandoch M, Dangwal S, Jobi K, Rauch BH, Doller A, Oberhuber A, Akhyari P, Schrör K, Fischer JW, Fender AC: Thrombin receptor protease-activated receptor 4 is a key regulator of exaggerated intimal thickening in diabetes mellitus. Circulation 130:1700-11 (2014)

Schrör K**:** Why we should not skip aspirin in cardiovascular prevention. Haemostseologie 35:Apr. 20 (2015)