6 Summary

Lipoxygenases are involved in many metabolic pathways of the organism. They play a major role in inflammation, tumor growth, angiogenesis and pathogenesis of atherosclerosis. Lipoxins are lipoxygenase products involved in the resolution of inflammation by inhibiting chemotaxis of leukocytes thus blocking the cascade of pro-inflammatory actions. So far, in the stomach this effect was described only for aspirin-triggered (R)epi-lipoxins which limit the gastric damage caused by aspirin. The present study deals with (S)lipoxins generated in the stomach during physiological and pathophysiological conditions and the enzymes of their synthesis, the lipoxygenases. Aim of the study was to investigate the role of lipoxins and lipoxygenases in gastric inflammation induced by ischemia-reperfusion or ethanol challenge and their contribution to the maintenance of mucosal integrity.

The gastric mucosa of rats was subjected to two different types of inflammation, an ischemia (30 min) - reperfusion (60 min) model and a model of ethanol-induced damage. Animals were treated with lipoxygenase inhibitors or a lipoxin A4 receptor antagonist and/or exogenous lipoxin A4. Afterwards expressions of lipoxygenases were tested using Real-Time-PCR, the amount of lipoxin A4 was examined via ELISA and LC-MS/MS and a lesion index was calculated as parameter for mucosal damage, respectively.

In addition to 5-lipoxygenase mRNA this was the first time 12/15-lipoxygenase mRNA was detected in the stomach. Further results demonstrate that in the stomach 5- and 12/15-lipoxygenase are constitutively synthesised enzymes with constant expression rates during ischemia-reperfusion. During ischemia-reperfusion, treatment with a 5-, 12- or 15-lipoxygenase inhibitor leads to a loss of mucosal integrity and a significant increase in 5- and 12/15-lipoxygenase mRNA expression compared to untreated controls. This could be interpreted as a compensation of the mucosa against the loss of mucosal integrity.

There was no difference in the amount of lipoxin A4 in incubated or homogenated gastric mucosal samples of sham operated animals and animals subjected to...
ischemia-reperfusion. Thus, ischemia-reperfusion is obviously not an sufficient stimulus to enhance lipoxin A\textsubscript{4} synthesis. Treatment with the 5-lipoxygenase inhibitor MK-886 does not lead to a significant reduction of the amount of lipoxin A\textsubscript{4} generated in the gastric mucosa but inhibited synthesis of leukotriene C\textsubscript{4}. Lipoxin A\textsubscript{4} and leukotriene C\textsubscript{4} are generated from the same 5-lipoxygenase product (leukotriene A\textsubscript{4}). Hence, the finding that inhibition of lipoxin A\textsubscript{4} synthesis could not be observed cannot be attributed to a lack of inhibitionary activity of MK-886 on 5-lipoxygenase. It is possible that in the stomach lipoxin A\textsubscript{4} represents only a minor part of products generated via the 5-lipoxygenase pathway. This does not exclude the possibility that this small part may contribute to the maintenance of mucosal integrity.

The functional role of lipoxygenases is demonstrated by the finding that during ischemia-reperfusion inhibition of 5-, 12- or 15-lipoxygenase leads to a significant dose-dependent aggravation of mucosal damage. Exogenous lipoxin A\textsubscript{4} antagonises this aggravation. Lipoxin A\textsubscript{4} has a general gastroprotective effect similar to prostaglandins, because exogenous lipoxin A\textsubscript{4} also counteracts the damage-aggravating effects of COX inhibitors. The importance of lipoxin A\textsubscript{4} for mucosal integrity is further supported by the observation that blockade of the lipoxin A\textsubscript{4} receptor during ischemia-reperfusion aggravates mucosal damage.

Additional results of this study demonstrate that mediators synthesised by the various lipoxygenases, probably lipoxin A\textsubscript{4}, are involved in mucosal protection against ulcerogenic substances during ischemia-reperfusion. Inhibition of a lipoxygenase or blockade of the lipoxin A\textsubscript{4} receptor potentiates the ulcerogenicity of certain noxious agents.

Certain parts of these results could be replicated in the model of ethanol-induced gastric damage. The adaptive protection of 20 \% ethanol against 70 \% ethanol is dose-dependently abolished by pretreatment with a lipoxygenase inhibitor or blockade of the lipoxin A\textsubscript{4} receptor. Furthermore, 5-, 12- and 15-lipoxygenase, respectively, are involved in the protection induced by Na-salicylate against celecoxib-induced damage in the model of adaptive gastroprotection. In contrast to the ischemia-reperfusion injury, exogenous lipoxin A\textsubscript{4} does not protect against ethanol-induced gastric mucosal damage, which is caused by a mechanism different
from ischemia-reperfusion damage. This, however, does not exclude the possibility of an involvement of endogenous lipoxin A₄ in mucosal protection against ethanol-induced damage.

Taken together, lipoxygenases and their product lipoxin A₄ are involved in the maintenance of mucosal integrity during various inflammationary conditions in the gastric mucosa.