STRESZCZENIE W JĘZYKU ANGIELSKIM (ABSTRACT)

Within this dissertation, the contribution of endogenous gaseous molecules, such as hydrogen sulfide (H_2S), carbon monoxide (CO) and nitric oxide (NO) in gastrointestinal (GI) physiology and pathophysiology was reviewed, described and compared. H_2S, in similar manner as CO and NO, modulates the plethora of fundamental biological functions. By regulating the molecular pathways and the activity of proteins (post-translational persulfidation), H_2S exerts anti-inflammatory, antioxidative and cytoprotective properties. Translational studies based on animal models of gastric mucosal injuries showed the gastroprotective effect of H_2S, both endogenously produced and released from pharmacological donors. Importantly, GI injuries evoked by the treatment with non-steroidal anti-inflammatory drugs (NSAIDs) represent a clinically significant challenge. Decreased gastric mucosal bioavailability of endogenous H_2S was observed to be involved in pathogenesis of NSAIDs-damage, However, the molecular background underlying this phenomenon has not been fully explored. Therefore, within this project, the new hybrid derivatives of ketoprofen (ATB-352) and indomethacin (ATB-344), enriched with H_2S-releasing moiety were implemented to explore new and confirm already identified modes of H_2S activity in GI tract. Based on animal models, it was observed that H_2S released from ATB-352 enhanced e.g., the expression of the suppressor of cytokine signalling (SOCS)3 and cAMP response element-binding protein (CREB), activating anti-inflammatory response in intestinal mucosa. Moreover, ATB-352, unlike “classic" ketoprofen did not cause significant changes of the intestinal microbiome profile. Increased/restored H_2S bioavailability inhibited the development of ketoprofen-induced, pathological gastric mucosal and intestinal injuries. Additionally, H_2S-releasing ATB-344, unlike “classic" indomethacin, exerted even gastroprotective activity counteracting oxidative damage induced by ischemia and reperfusion (I/R). Low dose of H_2S released from ATB-344 maintained the gastric mucosal biosynthesis of physiologically cytoprotective prostaglandin E_2. Taken together, altered H_2S signalling contributes to the development of GI pathologies. Increased/restored bioavailability of H_2S that was released from ATB-352 or ATB-344 interferes in pathogenesis of gastric and/or intestinal injuries, not only limiting adverse effects of NSAIDs but also enhancing defensive response of GI mucosal barrier to the functional deregulations of physiological oxidative balance.