

Histamine 3 Receptor and Angiotensin II Receptor Balance Regulates Cardiac Arrhythmias

In severe myocardial ischemia, norepinephrine (NE) is abundantly carried out of sympathetic nerve terminals by the NE transporter, neuronal Na^+/H^+ exchanger (NHE), and is a key arrhythmogenic determinant. Hashikawa-Hobara et al. investigated whether enhanced ischemic cardiac dysfunction, which is manifest when histamine H_3 receptors (H_3R) are blocked or deleted, results from an unimpeded angiotensin II receptor (AT_1R)-NHE activation. These studies have uncovered a novel cardioprotective action resulting from activation of neuronal H_3R in mammalian heart. Binding of an endogenous ligand to H_3R , most likely histamine, released by action of reactive oxygen species produced during ischemia/reperfusion, reduces the formation of diacylglycerol, diminishing protein kinase C activity. This in turn decreases NHE activity, causing intracellular acidification, and stimulates the production of nitric oxide (NO), which suppresses AT_1R expression. H_3R -induced decrease in NHE activity and increased NO synthesis may be responsible for decreased AT_1R protein abundance. These findings suggest that down-regulation of AT_1R signaling and attenuation of NE release by activation of neuronal H_3R are plausible mechanisms of cardioprotection, not only in myocardial ischemia but also in other cardiac dysfunctions in which ANG II plays a major role, such as heart failure.

See article at *J Pharmacol Exp Ther* 2012, **340**:185–191

Targeting the Arthritic Joint with Small Interfering RNA-Encapsulated Liposomes

Rheumatoid arthritis (RA) is characterized by chronic synovitis affecting multiple joints. Some forms of RA can be effectively treated with anti-TNF- α therapies. However, systemic treatment with anti-tumor necrosis factor- α (TNF- α) therapies can result in an impaired immune system and opportunistic infection; therefore, targeting therapies to the inflamed joints could avoid some of these systemic toxicities. Komano et al. evaluated the accumulation of small interfering RNA (siRNA)-encapsulated liposomes in inflamed joints and the therapeutic potential of these siRNA-encapsulated liposomes targeting TNF- α . Using a complex of the encapsulated liposome wrapsome (WS) and Cy5-labeled siRNA (siRNA/WS), higher fluorescence was observed in the inflamed joints versus normal tissues and in synoviocytes versus splenocytes/bone marrow/peripheral blood leukocytes. The majority of Cy5-positive synoviocytes were CD11b^+ , primarily macrophages and neutrophils. With the TNF- α targeting siRNA/WS, significant reductions in TNF- α mRNA and severity of the arthritis in the joints were observed. The siRNA/WS was mainly incorporated into CD11b^+ cells, including macrophages and neutrophils, in the inflamed synovium, suggesting its potential therapeutic effects in RA by silencing the expression of inflammatory molecules produced by these cells in the joint and not systemically.

See article at *J Pharmacol Exp Ther* 2012, **340**:109–113

Role of Neuronal Nitric-Oxide Synthase in Acetaminophen-Induced Hepatotoxicity

Acetaminophen (APAP; *N*-acetyl-*p*-aminophenol), a commonly used analgesic/antipyretic drug, when overdosed, produces a centrilobular hepatic necrosis and hepatotoxicity driven predominantly by oxidative stress. Agarwal et al. studied the role of neuronal nitric-oxide synthase (nNOS) in APAP-induced hepatotoxicity in nNOS knockout (KO) and wild-type (WT) mice. APAP toxicity induced significant increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in WT mice as early as 4 h after dosing, whereas in nNOS KO mice, the increases were significantly delayed, occurring 8 h after dosing. However, there was no difference between WT and nNOS KO mice in terms of the ultimate histopathology of APAP hepatotoxicity. Because oxidative stress is regulated by manganese superoxide dismutase (MnSOD), it is interesting that MnSOD is the only nitrated protein in nNOS KO mice, which suggests that nitration of MnSOD is dependent on other NOS forms in the liver. Decreased MnSOD activity coincides with increased nitration of MnSOD and increased ALT release, suggesting that inhibition of MnSOD activity in APAP toxicity contributes to toxicity. These results indicate that the delay in the onset of hepatotoxicity in the nNOS KO mice compared with the WT mice suggests that nNOS plays an important role in initiation of APAP hepatotoxicity.

See article at *J Pharmacol Exp Ther* 2012, **340**:134–142

Glycogen Synthase Kinase 3β / β -Catenin Signaling but Not Hypoxia-Inducible Factor- 1α Contributes to Defective Renal Wound Healing during Hypoxia

During wound healing, hypoxia, partly as a result of vascular damage and decreased blood supply along with increased oxygen consumption of wounded cells, induces angiogenesis and tissue remodeling but may also affect the healing response of parenchymal cells. Peng et al. investigated whether and how hypoxia affects wound healing in parenchymal cells in injured organs, such as the kidneys. When renal proximal tubular cells (RPTC) are exposed to hypoxic conditions (1% oxygen), wound healing (scratch model) and migration are significantly slower. Hypoxia-inducible factor- 1α (HIF- 1α) was induced by wounding under normoxic and enhanced under hypoxic conditions; however, scratch-wound healing was not significantly affected by either pharmacological activation of HIF or genetic deletion of HIF-1. The induction of β -catenin during hypoxia is accompanied by glycogen synthase kinase 3β (GSK3 β) inactivation (possibly by Akt activation) and can be mimicked by pharmacological inhibition of GSK3 β . Significantly higher Akt activation was observed during wound healing under hypoxia. These results suggest that hyperactivation of Akt by wound healing in hypoxic cells may inactivate GSK3 β , resulting in the induction of β -catenin to prevent wound healing in renal tubular cells under hypoxia.

See article at *J Pharmacol Exp Ther* 2012, **340**:176–184