Highlighted Papers

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor Activation Induces Dystonia in Mice

Dystonia, the third most common movement disorder after tremor and Parkinson's disease, is characterized by involuntary muscle contractions that cause debilitating twisting movements and postures. Human functional imaging studies associate cerebellar hyperactivity with dystonia. Fan et al. explored the relationship between abnormal cerebellar excitation and dystonia to determine whether a nonspecific increase in excitability or specific pathways were involved with dystonia. Nonspecific increase in cerebellar excitability (induced by picrotoxin) was not associated with dystonia. Instead, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (glutamate) receptor activation was necessary to evoke dystonia. AMPA agonists induced, antagonists reduced, and AMPA desensitization reduced dystonia. AMPA antagonists also reduced dystonia in the dystonic mouse mutant *tottering*, suggesting a link in other genetic models of dystonia. These animal studies, coupled with the results from imaging and blood flow studies, suggest a novel hypothesis that the increase in cerebellar signal observed in neuroimaging studies of patients with dystonia may be an indirect reflection of abnormal AMPA receptor activation. The obvious correlate of this hypothesis is that reducing AMPA receptor signaling by directly blocking AMPA receptors, promoting AMPA receptor desensitization or negative allosteric modulation of AMPA receptors, may prove useful in the treatment of dystonia.

See article at *J Pharmacol Exp Ther* 2012, **340:**733–741.

Activated Endothelial Targeting of Nanocarriers with Fibrinogen-Derived Peptides

Intercellular adhesion molecule-1 (ICAM-1), a transmembrane glycoprotein and coreceptor for leukocyte integrins, is overexpressed in inflammation, thrombosis, oxidative stress, metabolic diseases, and various genetic conditions; therefore, ICAM-1 represents a target for delivery of drug carriers to areas affected by disease. To mitigate the obstacles of long-term use of antibody-coated nanocarriers for treatment, Garnacho et al. evaluated polymer nanocarriers targeted to ICAM-1 by a 17-mer linear peptide derived from the ICAM-1-binding sequence of fibrinogen, γ3. These results show that γ3 nanocarriers target ICAM-1 with efficiency and specificity similar to that of anti-ICAM nanocarriers. Furthermore, γ3 nanocarriers are internalized by cells in culture and in vivo and transported to lysosomes via cell adhesion molecule (CAM)-mediated endocytosis, without apparent disruption of cell junctions, similar to anti-ICAM counterparts. These results show that model polymer nanocarriers coated with γ3 efficiently and specifically bind to both human and mouse ICAM-1. This provides targeting and intracellular transport similar to that of anti-ICAM NCs previously reported, offering a new opportunity to advance the design of translational ICAM-1-targeting platforms in the preclinical and, perhaps, future clinical realm.

See article at *J Pharmacol Exp Ther* 2012, **340:**638–647.

Regulating Hepatocyte Growth Factor/Met Signaling with Angiotensin IV Analogs

Dysregulation of the hepatocyte growth factor (HGF)/Met system often leads to neoplastic changes and to cancer. Kawas et al. reported previously that hexapeptides derived from the HGF hinge binding region mimicked the effects of norleual [Nle-Tyr-Leu-Ψ-(CH_2-NH_2)$^{3-4}$-His-Pro-Phe], an angiotensin (Ang) analog (*J Pharmacol Exp Ther* 2011, **339:**509–518). However, norleual is highly unstable, which makes its transition to clinical use problematic. Kawas et al. developed a family of metabolically stabile Ang IV-related analogs referred to as the 6-AH family. The 6-AH family had an improved half-life relative to norleual ($t_{1/2}$ of 80 versus < 5 min), mimicked the dimerization domain HGF (hinge region), and attenuated the capacity of HGF to activate Met. The 6-AH family member with cysteine at the 2 position was a particularly effective antagonist of HGF-dependent cellular activities. Reduction in pulmonary colonization by B16-F10 melanoma cells demonstrated the efficacy of this stable analog of Ang IV. These studies highlight the ability of Ang IV-like molecules to bind to HGF, block HGF dimerization, and inhibit the HGF/Met system. Moreover, these data encourage the development of Ang IV-related pharmaceuticals as therapeutic agents in disorders for which inhibition of the HGF/Met system would be clinically advantageous.

See article at *J Pharmacol Exp Ther* 2012, **340:**539–548.

Neuropathic Pain through Epigenetic Augmentation of the Macrophage Inflammatory Protein 2/C-X-C Chemokine Receptor Type 2 Axis

Neuropathic pain occurs as a result of damage and/or inflammation in the nervous system and presents as severe chronic pain. Neuroinflammation mediated by chemokines may be associated with the pathogenesis of neuropathic pain. Kiguchi et al. investigated the roles of the C-X-C chemokine ligand type 2 [macrophage inflammatory protein 2 (MIP-2)] and C-X-C chemokine receptor type 2 (CXCR2) in nerve injury-induced neuropathic pain. Expression of MIP-2 and CXCR2 were up-regulated and localized on accumulated neutrophils and macrophages in the injured sciatic nerve (SCN) after partial sciatic nerve ligation (PSL). MIP-2-neutralizing antibody or the CXCR2 antagonist *N*-(2-bromophenyl)-*N*′-(2-hydroxy-4-nitrophenyl)urea (SB225002) prevented PSL-induced tactile allodynia and thermal hyperalgesia. Both anti-MIP-2 and SB225002 suppressed up-regulation of inflammatory cytokines and chemokines in the injured SCN. Acetylation of histone H3 (AcK9-H3) on the promoter region of MIP-2 and CXCR2 was increased in the injured SCN after PSL. This study demonstrates that expression of MIP-2 and CXCR2 was up-regulated by epigenetic histone H3 acetylation in recruited macrophages and neutrophils localized in the injured peripheral nerves. Augmentation of the MIP-2/CXCR2 axis recruited neutrophils into the injured nerves and elicited neuroinflammation, which leads to neuropathic pain, suggesting that the MIP-2/CXCR2 axis could be a possible therapeutic target for the treatment of neuropathic pain.

See article at *J Pharmacol Exp Ther* 2012, **340:**577–587.