Highlighted Papers

Link between Neuropeptides, Renin-Containing Mast Cells, and Cardiac Arrhythmic Dysfunction

In ischemia/reperfusion, mast cells can release renin initiating activation of local renin-angiotensin system, ultimately leading to the production of angiotensin II and norepinephrine (NE) and mediating severe arrhythmic dysfunction. Morrey et al. set out to determine whether neuropeptides released from sensory nerve cells during ischemia/reperfusion were responsible for the release of renin from mast cells. Sensory nerves are juxtaposed to cardiac mast cells, and stimulation of sensory C-fibers releases calcitonin gene-related peptide (CGRP) and substance P, which in turn is accompanied by an overflow of renin and NE. The release of renin and NE is prevented by mast cell stabilizers and pharmacological blockage of substance P and CGRP receptors; whereas NE release is blocked by an angiotensin receptor (AT1) antagonist that itself does not prevent the release of renin. Coupled to the in vitro ability of substance P to elicit mast cell renin release and that ischemia/reperfusion elicits substance P and CGRP release followed by renin and NE, which is accompanied by sustained reperfusion arrhythmias, supports the hypothesis that in the heart the link between sensory C-fibers and cardiac mast cells is the release of neuropeptides.

See article at *J Pharmacol Exp Ther* 2010, **335:**76–84.

Afucosylated Anti-CD19 Antibody and B-Cell Depletion

Monoclonal antibody targeting of cell surface CD20 on B-cell malignancies by rituximab (Rituxan) has been a promising therapy for several hematological malignancies. However, many of these patients relapse after treatment. Herbst et al. investigated the ability to target B-cell surface CD19 and improve the antibody-directed cellular cytotoxicity (ADCC) by using an afucosylated form of the monoclonal antibody (mAb). MEDI-551 is a new afucosylated anti-CD19 mAb optimized for enhanced ADCC. MEDI-551 depletes B cells at lower mAb doses than rituximab and was more effective at depleting blood and tissue B cells in a double transgenic mouse model. Unlike rituximab, MEDI-551 does not rely on complement-dependent cytotoxicity for part of its efficacy. MEDI-551 also resulted in extended B-cell depletion from blood and spleen relative to rituximab treatment, probably due to bone marrow B-cell depletion. MEDI-551 represents a new anti-CD19 mAb with enhanced ADCC function that has potential as a new form of treatment for B-cell malignancies and potentially B-cell-dependent autoimmune diseases.

See article at *J Pharmacol Exp Ther* 2010, **335:**213–222.

TAK-348, Longer Lasting Inhibition of Gastric Acid Secretion through Potassium-Competitive Acid Blockage

Proton pump inhibitors (PPIs) are widely used in the treatment of acid-related diseases such as gastroesophageal reflux disease; however, rapid symptom relief and suppression of night time acid secretion remain unmet medical needs. Another class of acid blockers is the potassium-competitive acid blockers (P-CABs), Hori et al. describe the discovery of new, potent, and long acting P-CAB, TAK-438 [1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine monofumarate]. Unlike lansoprazole, a typical PPI, or SCH28080 [3-(cyanomethyl)-2-methyl,8-(phenylmethoxy)imidazo(1,2-*a*)pyridine], an early-generation P-CAB, TAK-438, was unaffected by ambient pH, reversible like SCH28080, more potent in vivo, and completely inhibited basal and stimulated gastric acid secretion in rats, and its effect was sustained longer than either agent in vivo. Given that TAK-438 is a pyrrole derivative with a chemical structure that is completely different from other P-CABs developed to date along with superior properties to other P-CABs, TAK-438 has the potential to have improved efficacy and avoid hepatotoxicity observed with predecessor P-CABs. TAK-438 may provide a new option for patients whose acid-related disease is refractory or inadequately controlled by PPIs.

See article at *J Pharmacol Exp Ther* 2010, **335:**231–238.

Altered Ethanol Sensitivity of Hippocampal Interneurons between Adolescents and Adults

Hippocampal $GABA_A$ receptor-mediated synaptic function is highly sensitive to ethanol (EtOH), and behaviorally relevant concentrations increase inhibitory postsynaptic currents in hippocampal CA1 and CA3 pyramidal cells regulated by EtOH-induced spontaneous firing of interneurons. Yan et al. compared interneuron firing in both the stratum lacunosum moleculare (SLM) and the stratum oriens (SO) in adolescent and adult rats. Based on their previous work in the SLM, EtOH promotes firing on SLM interneurons more potently in adolescent than adult interneurons; however, in the present study, EtOH promotes greater firing in adult interneurons in the SO, thus implying developmental regulation of sensitivity to EtOH. The developmental mediation of those effects is distinct among different populations of interneurons in area CA1 of the hippocampus, suggesting that SO and SLM interneurons mature differentially in some essential way that regulates EtOH sensitivity. These studies suggest that more intensive studies on interneurons in the context of adolescent EtOH sensitivity are needed. As classification of interneurons has identified four major groups and 12 distinct cell types, it will be challenging to identify the interneuron population(s) responsible for this differential sensitivity to EtOH.

See article at *J Pharmacol Exp Ther* 2010, **335:**51–60.