Highlighted Papers

Differential Pathway Coupling Drives Selectivity of an Insulin Receptor Agonist

The monoclonal antibody XMetA is an allosteric partial agonist of the insulin receptor (IR) that activates the "metabolic" Akt kinase signaling pathway while having little or no effect on the "mitogenic" extracellular signal-regulated kinase (ERK) signaling pathway. To investigate the nature of this selective signaling, a detailed investigation of XMetA was conducted to evaluate specific phosphorylation and activation of IR, Akt, and ERK in CHO cell lines expressing the human IR. Maximally effective concentrations of XMetA were sufficient for robust Akt phosphorylation, but had little effect on ERK phosphorylation. These data indicate that the "preferential signaling" of XMetA is due to an innate difference in pathway sensitivity of Akt versus ERK responses to IR activation and partial agonism by XMetA, rather than a separate pathway-biased mechanism. The metabolic selectivity of partial IR agonists, like XMetA, may be a desirable feature of therapeutic agents designed to regulate blood glucose levels while minimizing undesirable outcomes of excessive IR mitogenic activation.

See article at *J Pharmacol Exp Ther* 2015, **353**:35–43.

A Fast Skeletal Troponin Activator Improves Exercise Tolerance in Heart Failure

Heart failure–mediated skeletal myopathy often manifests as dyspnea and limb muscle fatigue. The objective of this study was to investigate the effect of a fast skeletal troponin activator, CK-2127107 (2-aminoalkyl-5-*N*-heteroarylpyrimidine), on skeletal muscle function and exercise performance in rats exhibiting heart failure–mediated skeletal myopathy. Rats underwent coronary artery ligation resulting in myocardial infarction and a progressive decline in cardiac function [left anterior descending coronary artery heart failure (LAD-HF)]. LAD-HF rat hindlimb and diaphragm muscles exhibited muscle atrophy, and fatigability was increased during repeated in situ isokinetic plantar flexor muscle contractions. CK-2127107 produced a leftward shift in the force-Ca^{2+} relationship of diaphragm and extensor digitorum longus fibers. In the LAD-HF rats, a single oral dose of CK-2127107 increased rotarod running time. In summary, CK-2127107 increases exercise performance in this heart failure model, suggesting that modulation of skeletal muscle function by a fast skeletal troponin activator may be a useful therapeutic in heart failure–associated exercise intolerance.

See article at *J Pharmacol Exp Ther* 2015, **353**:159–168.

Interaction between Bupropion and MDMA

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a popular recreational drug. This study explored the role of dopamine in the psychotropic effects of MDMA using bupropion to inhibit the transporters through which MDMA releases dopamine and norepinephrine. The pharmacodynamic and pharmacokinetic interactions between bupropion and MDMA were studied in healthy subjects. Bupropion reduced the MDMA-induced elevations in plasma norepinephrine concentrations and the heart rate response to MDMA. In contrast, bupropion increased plasma MDMA concentrations and prolonged its subjective effects. Conversely, MDMA increased plasma bupropion concentrations. The results indicate a role for the transporter-mediated release of norepinephrine in the cardiostimulant effects of MDMA, but do not support a modulatory role for dopamine in the mood effects of MDMA. The results also indicate that the use of MDMA during therapy with bupropion may result in higher plasma concentrations of both MDMA and bupropion, and enhanced mood effects but lower cardiac stimulation.

See article at *J Pharmacol Exp Ther* 2015, **353**:102–111.

Control of Ethanol Sensitivity of the Glycine Receptor α3 Subunit

Studies have shown that the effect of ethanol on glycine receptors (GlyRs) containing the α1 subunit is affected by interaction with heterotrimeric G proteins ($G\beta\gamma$). It is unknown, however, whether ethanol affects the function of GlyRs containing the α3 subunit. Electrophysiological experiments showed that GlyR α3 subunits were not potentiated by pharmacological concentrations of ethanol or by $G\beta\gamma$. Mutation of corresponding glycine 254 in transmembrane domain 2 (TM2) found in α1 in the $\alpha3^{A254G}$–α1 chimera induced a glycine-evoked current that displayed potentiation during application of ethanol and $G\beta\gamma$ activation. Interestingly, insertion of the intracellular α3L splice cassette into GlyR α1 abolished the enhancement of the glycine-activated current by ethanol and activation by $G\beta\gamma$. These data demonstrate that GlyR α3 subunits are not modulated by ethanol. Residue A254 in TM2, the α3L splice cassette, and the C terminus domain of α3 GlyRs are determinants for low ethanol sensitivity and form the molecular basis of subtype-selective modulation of GlyRs by alcohol.

See article at *J Pharmacol Exp Ther* 2015, **353**:80–90.