Sildenafil Does Not Prevent Cardiomyocyte Remodeling Induced by AT1R Signaling

Mouse models imply that the phosphodiesterase 5 inhibitor sildenafil (SIL), via increasing cGMP, protects against angiotensin II (Ang II) stimulated cardiac remodeling. It is unclear which cell types are involved in these effects, because Ang II may exert its adverse effects by modulating multiple reno-vascular and cardiac functions via Ang II type 1 receptors (AT1R). In this study, to test the hypothesis that SIL/cGMP opposes cardiac stress provoked by amplified Ang II/AT1R directly in cardiomyocytes (CMs), transgenic mice with CM-specific overexpression of the AT1R under the control of the α-myosin-heavy chain promoter (αMHC-AT1Rtg/1) were studied. The extent of cardiac growth was assessed in absence or presence of SIL. Prolonged SIL treatment did not limit the progressive CM growth, fibrosis or decline in cardiac functions in the αMHC-AT1Rtg/1 model suggesting that SIL does not interfere with the pathogenic actions of amplified AT1R signaling in CMs.


Claudin-1 Binder Enhances Epidermal Permeability in a Human Keratinocyte Model

Modulation of the tight junction (TJ) seal is a promising option for increasing the transdermal absorption of drugs. The binding of the claudin (CLDN) family of tetra-transmembrane proteins through cis- and trans-interactions is an integral part of seal formation. Because epidermal TJs contain CLDN-1 and -4, a binder for these CLDNs may be a useful modulator of the permeability of the epidermal barrier. The present study investigated whether m19, which can bind to CLDN-1/4, modulates the integrity of epidermal TJs and the permeability of cell sheets to solutes. Treatment of normal human epidermal keratinocytes (NHEKs) with m19 reduced the integrity of TJs. A CLDN-1–specific binder (7A5) also weakened the TJ seal in NHEKs. Treatment of NHEKs with 7A5 enhanced permeation of a paracellular permeation marker. These findings indicate that CLDN-1 is a potential target for modulating the permeability of the epidermis and that 7A5 is a promising candidate molecule for development as a dermal absorption enhancer.

See article at J Pharmacol Exp Ther 2015, 354:440–447.

Mathematical Modeling of Cellular Responses to Bortezomib

Systems models of biological networks show promise for informing drug target selection/qualification, identifying lead compounds and factors regulating disease progression, rationalizing combinatorial regimens, and explaining sources of inter-subject variability and adverse drug reactions. In this study, logic-based modeling of signal transduction pathways in U266 multiple myeloma (MM) cells was used to guide the development of a simple dynamical model linking bortezomib exposure to cellular outcomes. Bortezomib is a commonly used first-line agent in MM treatment; however, knowledge of the signal transduction pathways regulating bortezomib-mediated cell cytotoxicity is incomplete. A Boolean network model of 66 nodes was constructed that includes major survival and apoptotic pathways and was updated using responses to several chemical probes. Simulated responses to bortezomib were in good agreement with experimental data, and a reduction algorithm was used to identify key signaling proteins.

See article at J Pharmacol Exp Ther 2015, 354:448–458.

Pregnane X Receptor-Humanized Mice and Acute Ethanol Hepatotoxicity

Females are more susceptible to developing alcoholic liver disease following chronic ethanol (EtOH) ingestion. However, little is known about the relative effects of acute EtOH exposure on hepatotoxicity in female versus male mice. The nuclear receptor pregnane X receptor (PXR) is a broad-specificity sensor with species-specific responses to toxic agents. In this study, to examine the effects of the human PXR on acute EtOH toxicity, the responses of male and female PXR-humanized (hPXR) transgenic mice administered oral binge EtOH were analyzed. hPXR females expressed higher levels of enzymes responsible for EtOH metabolism and key mediators of hepatocyte replication and repair. EtOH ingestion upregulated hepatic estrogen receptor α, cyclin D1, and CYP2E1 in both genders, but differentially altered lipid and EtOH metabolism. Consistent with higher basal levels of EtOH metabolizing enzymes, blood EtOH was more rapidly cleared in hPXR females. These factors combined to provide greater protection against EtOH-induced liver injury in female hPXR mice.