Highlighted Papers

**Tonic Inhibition of G Protein–Coupled Receptor Kinase 2 of Endothelial Protein Kinase B/Endothelial Nitric-Oxide Synthase Signaling**

We tested the hypothesis that G protein–coupled receptor kinase 2 (GRK2) may be an important contributor to vascular endothelial dysfunction in diabetes. Human umbilical venous endothelial cells (HUVECs) were exposed to high glucose and high insulin (HG/HI) to mimic insulin-resistant diabetic conditions. GRK2 expression and membrane translocation were upregulated under HG/HI conditions. HG/HI did not modify activation of protein kinase B (Akt) and endothelial nitric-oxide synthase (eNOS), but GRK2 inhibition or small interfering RNA resulted in an increase in Akt and eNOS activation in HUVECs exposed to HG/HI. Our studies reveal that GRK2, which is upregulated by HG/HI, leads to a tonic inhibition of the insulin Akt/eNOS pathway in endothelial cells, providing new insight into the pathogenesis of diabetes-associated endothelial dysfunction.


**Clinical and Preclinical Characterization of a Histamine H4 Antagonist**

JNJ-39758979 ([R]-4-(3-amino-pyrrolidin-1-yl)-6-isopropylpyrimidin-2-ylamine) is a potent histamine H4 receptor (H4R) antagonist with a Ki at the human receptor of 12.5 nM and greater than 80-fold selectivity over other histamine receptors. JNJ-39758979 showed dose-dependent activity in models of asthma and dermatitis, consistent with other H4R antagonists. Preclinical toxicity studies of up to 6 months in rats and 9 months in monkeys indicated an excellent safety profile supporting the clinical testing of the compound. An oral formulation of JNJ-39758979 was studied in a phase 1 human volunteer study to assess safety, pharmacokinetics, and pharmacodynamics. The compound was well tolerated with the exception of dose-dependent nausea, and it exhibited good pharmacokinetics after a single oral dose with a plasma half-life of 124 to 157 hours. Dose-dependent inhibition of histamine-induced eosinophil shape change was detected, suggesting that the H4R was inhibited in vivo.


**Tolvaptan Delays the Onset of End-Stage Renal Disease in Polycystic Kidney Disease**

Tolvaptan, a selective vasopressin V2 receptor antagonist, slows the increase in total kidney volume and the decline in kidney function in patients with polycystic kidney disease (PKD). However, it is unclear whether tolvaptan was able to delay progression to end-stage renal disease (ESRD). The present study examined the effects of short-term and long-term treatment in DBA/2FG-pcy mice, a model of nephronophthisis. With short-term treatment from 5 to 15 weeks of age, tolvaptan enhanced aquaresis, prevented increases in kidney weight and cyst volume, and was associated with significant reductions in kidney cyclic AMP levels and extracellular signal–regulated kinase activity. With long-term treatment from 5 to 29 weeks of age, tolvaptan attenuated the increase in kidney volume, reduced urinary albumin excretion, and reduced mortality to 20% compared with 60% in the control subjects. These data indicate that tolvaptan may delay the onset of ESRD in PKD by suppressing the increases in kidney volume and renal injury.

See article at *J Pharmacol Exp Ther* 2014, 349:258–267.

**Intermittent Cocaine Administration Produces Sensitization of Stimulants at the Dopamine Transporter**

Previous studies investigating adaptations following cocaine self-administration have shown that the development of reduced cocaine potency at the dopamine transporter (DAT) results from high, continuous levels of intake (long access, LgA), whereas sensitization of cocaine potency is caused by intermittent patterns of cocaine administration (intermittent access, IntA). Here we determined whether the changes observed following cocaine self-administration were specific to cocaine or translated to other psychostimulants. We assessed the potency of amphetamine, a releaser, and methylphenidate (MPH), a DAT blocker that is functionally similar to cocaine and structurally related to amphetamine. MPH and amphetamine potencies were increased following IntA, whereas neither was changed following LgA. This demonstrates that the pattern with which cocaine is administered determines the neurochemical consequences of cocaine and the sensitization of other psychostimulants.