Highlighted Papers

Behavioral Effects and Pharmacokinetics of MDMA (Ecstasy) in Baboons
(±)-3,4-Methylenedioxymethamphetamine HCl (MDMA, Ecstasy) is a popular drug of abuse. This study characterized the behavioral effects of MDMA in a species closely related to humans. MDMA decreased food-maintained responding and increased bruxism. Drug blood level determination showed no MDMA after low doses and only modest levels following high doses. High metabolite levels were detected after all doses, suggesting extensive first-pass metabolism in the baboon. The present results demonstrate that MDMA produced behavioral effects in baboons that are similar to those reported in humans and that the blood levels of MDMA may not be predictive of the behavioral effects. Metabolites appear to play a role in the behavioral changes.

See article at J Pharmacol Exp Ther 2013, 345:342–353.

HCN1 Channels as Targets for Amelioration of Hyperalgesia in a Mouse Model of Pain
HCN channels constitute an attractive target for treating chronic pain. Analgesics targeting HCN1 must spare the cardiac pacemaker current, which is carried mostly by HCN2 and HCN4. The general anesthetic propofol selectively inhibits HCN1 channels versus HCN2–4. As a consequence, it was hypothesized that propofol and congeners should be antihyperalgesic. 2,6-Di-tert-butylphenol (2,6-DTBP) is more potent than propofol for HCN1 while maintaining selectivity over HCN2–4. In a peripheral nerve ligation model of neuropathic pain, 2,6-DTBP and subhypnotic propofol are antihyperalgesic. The findings are consistent with these compounds exerting analgesia via the HCN1 channel.

See article at J Pharmacol Exp Ther 2013, 345:363–373.

Bioimaging Real-Time PXR-Dependent mdr1a Gene Regulation
A mouse containing firefly luciferase (lUC) knocked into the mdr1a genomic locus allows noninvasive bioimaging of intestinal mdr1a gene expression in live animals. In the current study, we crossed mdr1a.lUC mice into the pxr knockout (pxr−/−) genetic background and injected mice with pregnenolone-16α-carbonitrile (PCN), a strong mouse pregnane X receptor (PXR) ligand, and two therapeutically relevant taxanes, paclitaxel and docetaxel. All three agents induced mdr1a.lUC expression (bioluminescence), but only PCN and docetaxel appeared to act primarily via PXR. These results demonstrate that the mdr1a.lUC bioimaging model can capture changes in mdr1 gene expression under conditions of repeated xenobiotic treatment in vivo.

See article at J Pharmacol Exp Ther 2013, 345:438–445.

Effects of New SGLT2 Inhibitor, Luseogliflozin, on Diabetic Nephropathy in T2DN rats
The study examined the effect of long-term control of hyperglycemia with a new SGLT2 inhibitor, luseogliflozin. Chronic treatment with luseogliflozin produced a sustained increase in glucose excretion and normalized blood glucose and HbA1c levels to the same level as seen in rats treated with insulin. It had no effect on blood pressure. T2DN rats treated with vehicle exhibited progressive proteinuria, a decline in glomerular filtration rate (GFR), focal glomerulosclerosis, renal fibrosis, and tubular necrosis. Control of hyperglycemia with luseogliflozin prevented the fall in GFR and reduced the degree of glomerular injury, renal fibrosis, and tubular necrosis. In contrast, control of hyperglycemia with insulin had no effect on the progression of renal disease in T2DN rats.

See article at J Pharmacol Exp Ther 2013, 345:464–472.