Highlighted Papers

Modulation of Peripheral μ-Opioid Analgesia by σ_1 Receptors

This article evaluates the effects of σ_1-receptor inhibition on μ-opioid-induced mechanical antinociception and constipation. σ_1-Knockout mice exhibited marked mechanical antinociception in response to μ-opioid analgesics at systemic doses that were inactive in wild-type mice and even unmasked the antinociceptive effects of the peripheral μ-opioid agonist loperamide. Likewise, treatment of wild-type mice with selective σ_1 antagonists potentiated antinociception. These effects were fully reversed by treatment with a σ_1 agonist. In contrast to its effects on nociception, σ_1-receptor inhibition did not alter fentanyl- or loperamide-induced constipation, a peripherally mediated nonanalgesic opioid effect. Therefore, σ_1-receptor inhibition may be used as a systemic or local adjuvant to enhanced peripheral μ-opioid analgesia without affecting opioid-induced constipation.

See article at *J Pharmacol Exp Ther* 2014, **348:**32–45.

A Dopamine Transporter Ligand That Functions as a Cocaine Antagonist

An *N*-butyl analog of benztropine, JHW007 [*N*-(*n*-butyl)-3α-[bis(4′-fluorophenyl)methoxy]-tropane], binds to dopamine transporters (DAT) but has reduced cocaine-like behavioral effects and antagonizes various effects of cocaine. For example, cocaine increased locomotion, whereas JHW007 [was minimally effective early but increased activity 24-hours after injection. JHW007 antagonized the locomotor-stimulant effect of cocaine. JHW007 blocked locomotor-stimulant effects of cocaine in both dopamine D_2 and CB_1 receptor knockout and wild-type mice, indicating a lack of involvement of these targets. Time-course data indicate that administration of JHW007 antagonized the locomotor-stimulant effects of cocaine within 10 minutes of injection, whereas occupancy at the DAT determined in vivo did not reach a maximum until 4.5 hours after injection. Overall, these findings suggest that JHW007 has cocaine antagonist effects that are deviate from its DAT occupancy.

See article at *J Pharmacol Exp Ther* 2014, **348:**106–115.

Benztropine Analogs as Antagonists of Methamphetamine Self-Administration

Atypical dopamine-uptake inhibitors have low abuse potential and may serve as leads for the development of cocaine-abuse treatments. Among them, the benztropine (BZT) derivatives, JHW007 [*N*-(*n*-butyl)-3α-[bis-(4′-fluorophenyl)methoxy]-tropane hydrochloride], AHN2-005 [*N*-allyl-3α-[bis(4′-fluorophenyl)methoxy]- tropane oxalate], and AHN1-055 [3α-[bis(4′-fluorophenyl)methoxy]-tropane hydrochloride], dose-dependently decreased cocaine self-administration without effects on food-maintained responding. The present study examined selectivity by assessing effects of self-administration of other drugs. As with cocaine, each BZT analog dose-dependently decreased maximal self-administration of *d*-methamphetamine. In contrast, they were inactive against heroin and ketamine self-administration. These results support development of atypical dopamine uptake inhibitors as medication for stimulant abuse.

See article at *J Pharmacol Exp Ther* 2014, **348:**174–191.

Inhibition of Renal Potassium Channel Can Cause Diuresis and Natriuresis

The renal outer medullary potassium (ROMK) channel is located at the apical membrane of epithelial cells lining the thick ascending loop of Henle and cortical collecting duct and plays an important role in kidney physiology by regulating salt reabsorption. Loss-of-function mutations in the human ROMK channel are associated with antenatal type II Bartter's syndrome, an autosomal recessive life-threatening salt-wasting disorder with mild hypokalemia. Although selective ROMK inhibitors would be expected to represent a new class of diuretic, this hypothesis had never been tested. A potent ROMK inhibitor caused concentration-dependent diuresis and natriuresis in normotensive rats and dogs. Unlike hydrochlorothiazide, the ROMK inhibitor did not cause significant urinary potassium loss or changes in plasma electrolyte levels. These data indicate that pharmacological inhibition of ROML has the potential for affording diuretic/natriuretic efficacy similar to that of clinically used diuretics but without dose limiting hypokalemia.

See article at *J Pharmacol Exp Ther* 2014, **348:**153–164.