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Selective Orexin-1 Receptor Antagonist Attenuates Stress-Induced Hyperarousal

A role for the orexin-1 receptor (OX1R) in emotional behavior is emerging. The present study characterizes the brain-penetrant OX1R antagonist, compound 56 [*N*-({3-[(3-ethoxy-6-methylpyridin-2-yl)carbonyl]-3-azabicyclo[4.1.0]hept-4-yl}methyl)-5-(trifluoromethyl) pyrimidin-2-amine]. Receptor binding studies demonstrated that compound 56 crossed the blood-brain barrier and occupied OX1Rs in the rat brain. While compound 56 did not alter sleep in wild-type mice, its administration in OX2R knockout mice selectively promoted rapid eye movement sleep, demonstrating target engagement. In a rat model of stress induced by cage exchange, the OX1R antagonist prevented prolongation of sleep onset without affecting sleep duration. In a rat model of panic vulnerability (involving disinhibition of the perifornical OX region), the compound attenuated sodium lactate–induced panic-like behaviors without altering baseline locomotor or autonomic activity. In conclusion, OX1R antagonism represents a novel therapeutic strategy for the treatment of various psychiatric disorders associated with stress.

See article at *J Pharmacol Exp Ther* 2015, **352**:590–601.

Effect of Memantine on Cough Reflex Sensitivity in Humans and Guinea Pigs

Cough is a common reason that outpatients seek medical attention, yet therapeutic options for cough lack efficacy and are limited by safety and abuse liabilities. Memantine is an *N*-methyl-D-aspartate receptor channel blocker used in the treatment of Alzheimer's disease. The goals of this study were to compare the antitussive effects of memantine, dextromethorphan, and codeine in guinea pigs, and to evaluate the effect of memantine in humans. In guinea pigs, memantine and codeine were both superior to dextromethorphan in the citric acid cough challenge model. Subsequently, healthy volunteers as well as adults with acute viral upper respiratory tract infection (URI) underwent capsaicin cough challenges after ingestion of memantine and matched placebo. In healthy volunteers, memantine significantly inhibited cough reflex sensitivity. In subjects with URI, responsiveness to capsaicin was markedly increased, and the inhibition of cough reflex sensitivity by memantine did not reach statistical significance ($P = 0.088$).

See article at *J Pharmacol Exp Ther* 2015, **352**:448–454.

Effects of Fexofenadine in Intestinal Inflammation

The aim of this study was to evaluate the effect of fexofenadine on intestinal inflammation. Fexofenadine significantly inhibited the upregulated expression of interleukin-8 (IL-8) in HCT116 and COLO205 cells stimulated with tumor necrosis factor-α. Fexofenadine suppressed nuclear factor-κB DNA-binding activity. In addition, the induction of endoplasmic reticulum stress markers, caspase-12 and p-eukaryotic initiation factor (eIF2)-α, was significantly suppressed by the pretreatment of fexofenadine. Administration of fexofenadine significantly reduced the severity of dextran sulfate sodium (DSS)–induced murine colitis, as assessed by the disease activity index, colon length, and histology. In addition, the DSS-induced phospho-IκB kinase activation was significantly decreased in fexofenadine-pretreated mice. Finally, fexofenadine significantly reduced the severity of colitis and the immunoreactivity of caspase-12 and p-eIF2-α in IL-10$^{-/-}$ mice. These results suggest that fexofenadine is a potential therapeutic agent for the treatment of inflammatory bowel disease.

See article at *J Pharmacol Exp Ther* 2015, **352**:455–461.

Sulfa Drugs Inhibit Sepiapterin Reductase and Chemical Redox Cycling

Sepiapterin reductase (SPR) catalyzes the reduction of sepiapterin to dihydrobiopterin (BH2), the precursor for tetrahydrobiopterin (BH4), a cofactor critical for nitric oxide biosynthesis and alkylglycerol and aromatic amino acid metabolism. SPR also mediates chemical redox cycling, catalyzing one-electron reduction of redox-active chemicals; rapid reaction of the reduced radicals with molecular oxygen generates reactive oxygen species (ROS). Using recombinant human SPR, sulfonamide- and sulfonylurea-based sulfa drugs were found to be potent noncompetitive inhibitors of both sepiapterin reduction and redox cycling. In PC12 cells, which generate catecholamine and monoamine neurotransmitters via BH4-dependent amino acid hydroxylases, sulfa drugs inhibited both BH2/BH4 biosynthesis and redox cycling mediated by SPR. These data suggest that SPR and BH4-dependent enzymes, are "off-targets" of sulfa drugs. The ability of the sulfa drugs to inhibit redox cycling may ameliorate ROS-mediated toxicity generated by redox active drugs and chemicals.

See article at *J Pharmacol Exp Ther* 2015, **352**:529–540.

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