Highlighted Papers

Morphine Glucuronidation and Glucosidation, Complementary Metabolic Pathways

Morphine-3-β-D-glucuronide and morphine-6-β-D-glucuronide are the major metabolites of morphine in humans. More recently, morphine-3-β-D-glucoside (M-3-glucoside) was identified in the urine of patients treated with morphine. Kinetic and inhibition studies using human liver microsomes and recombinant UDP-glucuronosyltransferases as the enzyme sources were used here to characterize the relationship between morphine glucuronidation and glucosidation. The data indicate that morphine glucuronidation and glucosidation occur as complementary metabolic pathways catalyzed by a common enzyme (UGT2B7). Glucuronidation is the dominant metabolic pathway because the binding affinity of UDP-glucuronic acid to UGT2B7 is higher than that of UDP-glucose.

See article at *J Pharmacol Exp Ther* 2014, **349:**126–137.

In Vitro Pharmacology of GS-5759, a Phosphodiesterase 4 Inhibitor and β_2 Agonist

Inhaled long acting β_2-adrenoceptor agonists, which act as bronchodilators, and the oral anti-inflammatory phosphodiesterase 4 (PDE4) inhibitor roflumilast are approved therapies for chronic obstructive pulmonary disease. This article describes the activity of a novel, bifunctional, small molecule (*R*)-6-[(3-{[4-(5-{[2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl) ethyl]amino}pent-1-yn-1-yl)phenyl]carbamoyl}phenyl)sulfonyl]-4-[(3-methoxyphenyl)amino]-8-methylquinoline-3-carboxamide (GS-5759) that has specific β_2 agonist and PDE4 inhibitory activity. GS-5759 demonstrated potent and full agonist activity at β_2 adrenoceptors (EC_{50} = 8 nM) and is a potent inhibitor of the PDE4 enzyme (IC_{50} = 5 nM). In cell assays, GS-5759 inhibited lipopolysaccharide-induced tumor necrosis factor-α production in human peripheral mononuclear cells with an IC50 of 0.3 nM and in human neutrophils formyl-methionyl-leucyl-phenylalanine-induced super oxide anion production with an IC50 of 3 nM. The β_2 antagonist, ICI 118551 [(2*R**,3*R**)-1-[(2,3-dihydro-7-methyl-1*H*-inden-4-yl)oxy]-3-[(1-methylethyl)amino]-2-butanol], shifted the IC_{50} in these cell assays to 4 and 38 nM, respectively, demonstrating the contribution of both β_2 agonist and PDE4 inhibitory activity to GS-5759.

See article at *J Pharmacol Exp Ther* 2014, **349:**85–93.

TRPV4 Activation Constricts the Bronchus via the Release of Cysteinyl Leukotrienes

Prior studies have demonstrated that the ion channel TRPV4 is functionally expressed in airway smooth muscle cells and that TRPV4 single nucleotide polymorphisms are associated with airflow obstruction in patients with chronic obstructive pulmonary disease. Isometric tension measurements in ex vivo airways were used to determine whether pharmacological activation of TRPV4 with GSK1016790 [*N*-((1*S*)-1-{[4-((2*S*)-2-{[(2,4-dichlorophenyl) sulfonyl]amino}-3-hydroxypropanoyl)-1-piperazinyl]carbonyl}-3-methylbutyl)-1-benzothiophene-2-carboxamide] would constrict human bronchial tissue. As predicted, TRPV4 activation in the human airway produces contractions that can be blocked by TRPV4 antagonists. It is noteworthy that TRPV4-dependent contractions were also blocked by a 5-lipoxygenase inhibitor and cysteinyl leukotriene 1 receptor antagonists. These results fail to support the hypothesis that TRPV4 in airway smooth muscle cells regulate airway contractility short term. Rather, they provide pharmacological evidence that TRPV4 activation causes human airway constriction that is entirely dependent upon the production of cysteinyl leukotrienes.

See article at *J Pharmacol Exp Ther* 2014, **349:**118–125.

Protective Effects of Acetaminophen on Ibuprofen-Induced Gastric Mucosal Damage

Acetaminophen has gastroprotective effects against lesions induced by nonsteroidal anti-inflammatory drugs in rats. To investigate the mechanisms involved, transcriptome analyses of the ibuprofen-damaged gastric mucosa were performed in the presence and absence of acetaminophen. Ingenuity pathway analysis (IPA) revealed that acetaminophen suppressed the pathways related to cellular assembly and inflammation, whereas they were activated by ibuprofen. On the basis of gene classifications from the IPA Knowledge Base, we identified five genes that were related to gastric damage and showed significant changes in gene expression. The expression of matrix metalloproteinase-13 (MMP-13) was the most reactive, showing strong induction by ibuprofen and suppression by acetaminophen. Moreover, MMP-13 inhibitors decreased ibuprofen-induced gastric damage. These results suggest that acetaminophen decreases ibuprofen-induced gastric mucosal damage and that the suppression of MMP-13 may play a role.

See article at *J Pharmacol Exp Ther* 2014, **349:**165–173.