Highlighted Papers

Spleen Tyrosine Kinase Selective Inhibitor and Treatment of Rheumatoid Arthritis

Spleen tyrosine kinase (Syk) is broadly involved in regulating leukocyte immune function, principally by facilitating cellular activation in response to receptor engagement of antigen or of immune complex. Coffey et al. report on the discovery and characterization of (4-(3-(2*H*-1,2,3-triazol-2-yl)phenylamino)-2-((1*R*, 2*S*)-2-aminocyclohexylamino) pyrimidine-5-carboxamide acetate (P505-15), a novel, highly specific and potent orally available small-molecule inhibitor of Syk; they test the hypothesis that specific pharmacological inhibition of Syk kinase activity is sufficient to modulate leukocyte immune function and ameliorate inflammation in vivo. P505-15 potently and specifically inhibited Syk kinase activity in vitro (including whole blood assays), and ex vivo after oral dosing of P505-15, without inhibiting Syk-independent signaling. Submicromolar concentrations in blood, predicted to result in 67% inhibition of Syk, led to statistically significant anti-inflammatory effects in the mouse collagen antibody-induced arthritis (CAIA) and the rat collagen-induced arthritis (CIA) models. Syk kinase inhibition by P505-15 mimics the immunomodulatory phenotype of Syk knockout observed in other rodent models of rheumatoid arthritis. These data suggest that the specific inhibition of Syk may be a sufficient and safe strategy to control immune function in inflammatory diseases. P505-15 is currently in clinical development for the treatment of inflammatory diseases.

See article at *J Pharmacol Exp Ther* 2012, **340:**350–359.

Treating Asthma with Prostaglandin D_2 Receptor Antagonists

On mast cells, prostaglandin D_2 (PGD_2) and its receptor D prostanoid receptor 2 (DP_2) have been linked to the development of allergic inflammation, which has spurred interest in identifying more potent and selective antagonists of this receptor to treat asthma and related disorders. Pettipher et al. describe the pharmacological profile of (5-fluoro-2-methyl-3-quinolin-2-ylmethyl-indo-1-yl)-acetic acid (OC000459), an indole-1-acetic acid derivative and a potent and selective DP_2 antagonist. OC000459 potently displaces PGD_2 from DP_2 but does not interfere with the ligand-binding properties or functional activities of other prostanoid receptors. OC000459 competitively antagonized eosinophil shape-change responses induced by PGD_2. OC000459 inhibited activation of T helper 2 (Th2) cells and eosinophils in response to supernatants from IgE/anti-IgE activated human mast cells. OC000459 was orally bioavailable in rats and inhibited blood eosinophilia and airway eosinophilia in response to 13,14-dihydro-15-keto-PGD_2. OC000459 is a highly potent, selective, and orally active DP_2 antagonist that inhibits mast cell-dependent activation of Th2 cells and eosinophils. This compound is proving to be an excellent tool in defining the role of DP_2 in asthma and related allergic disorders. It is currently being evaluated in phase IIb trials and has the potential to be one of a new class of oral anti-inflammatory agents to treat allergic disorders.

See article at *J Pharmacol Exp Ther* 2012, **340:**473–482.

Mutations of the α1 Glycine Receptor Subunit Regulate Sensitivity to Alcohols

Glycine receptors (GlyRs) are inhibitory ligand-gated ion channels, and ethanol has the ability to potentiate glycine activation of the GlyR. Borghese et al. investigated the putative binding sites for alcohol (alteration of ethanol sensitivity) by introducing two mutations in the GlyR α1 subunit, M287L [transmembrane domain (TM) 3] and Q266I (TM2). Both mutants showed a reduction in glycine sensitivity and glycine-induced maximal currents. Activation by taurine, another endogenous agonist, was almost abolished in the M287L GlyR. Zinc enhancement of ethanol potentiation of glycine responses was absent in M287L GlyRs. Survival of homozygous knockin mice was impaired, and electrophysiological features of isolated neurons in the brain stem showed decreased glycine-mediated currents and decreased ethanol potentiation. This study suggests that many of the basic characteristics, such as channel properties, present in mutated GlyRs expressed in *Xenopus laevis* oocytes and human embryonic kidney 293 cells were similar to those observed in isolated neurons and membrane preparations from the corresponding knockin mice: 1) a small but general impairment of glycine action, most evident in the glycine-induced maximal currents, and 2) lack of sensitivity to ethanol.

See article at *J Pharmacol Exp Ther* 2012, **340:**304–316.

Knockin of Mutated α1 Glycine Receptor Subunits Alters Sensitivity to GABAergic Drugs

Alcohol actions on recombinant glycine receptors (GlyRs) showed that mutations M287L and Q266I of the α1 subunit lead to a reduction in ethanol potentiation of glycine-induced current. Blednov et al. constructed knockin mice with each of these mutations, allowing the use of behavioral testing to determine the influence of these changes on behavioral effects of ethanol and other drugs. Rotarod ataxia was one behavioral effect of ethanol reduced more in the Q266I mutant than the M287L mutant. Mutant mice also differed in ethanol consumption, ethanol-stimulated startle response, signs of acute physical dependence, and duration of loss of righting response produced by ethanol, butanol, ketamine, pentobarbital, and flurazepam. Some of these behavioral changes were mimicked in wild-type mice by acute injections of low, subconvulsive doses of strychnine. Both mutants showed increased acoustic startle response and increased sensitivity to strychnine seizures. In addition to reducing ethanol action on the GlyRs, these mutations reduced glycinergic inhibition, which may also alter sensitivity to GABAergic drugs. These results show the ability of a single amino acid change in the GlyR α1 subunit to decrease specific behavioral actions of ethanol and to alter other nonethanol behaviors, demonstrating the importance of GlyR function in diverse neuronal systems.

See article at *J Pharmacol Exp Ther* 2012, **340:**317–329.