Highlighted Papers

MPO Inhibition Prevents Immune Complex Vasculitis and Anti–Glomerular Basement Membrane Diseases

Small vessel vasculitis is a life-threatening condition, and patients typically present with renal and pulmonary injury. Disease pathogenesis is associated with neutrophil accumulation, activation, and oxidative damage; the latter being driven, in large part, by myeloperoxidase (MPO). PF-1355 [2-(6-(2,5-dimethoxyphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)acetamide] is a selective 2-thioracil mechanism-based MPO inhibitor. In this study, a pharmacokinetic/pharmacodynamic response model of PF-1355 exposure in relation with MPO activity was derived from mouse peritonitis. The contribution of MPO activity to vasculitis was then examined in an immune complex model of pulmonary disease. Oral administration of PF-1355 reduced plasma MPO activity, vascular edema, neutrophil recruitment, and elevated circulating cytokines. In a model of anti–glomerular basement membrane disease, albuminuria and chronic renal dysfunction were completely suppressed by PF-1355 treatment. These studies showed that MPO activity is critical in driving immune-complex vasculitis and provides confidence in testing the hypothesis in the clinic.

See article at *J Pharmacol Exp Ther* 2015, **353**:288–298.

Antialbuminuric Effects of the Angiotensin-Converting Enzyme Inhibitor Enalapril

The present study investigated the effect of enalapril on the glomerular sieving coefficient of albumin (GSC,\(\alpha\)) using intravital multiphoton microscopy. Munich Wistar Frömter (MWF) rats were used as a model of hypertension-related glomerular lesions. Young rats were nonproteinuric; however, the urinary albumin excretion gradually increased during aging, averaging 0.0051 mg/mOsmol per liter at 52 weeks. The albuminuria in aged MWF rats was accompanied by structural changes, which were indicative of glomerular lesions. The GSC,\(\alpha\) was low in young rats but increased markedly during aging, averaging 0.00057 in young and 0.0027 in 52-week-old rats. The treatment of proteinuric 12-month-old rats with enalapril over a 4-week period reduced the GSC,\(\alpha\) from 0.0027 to 0.0013. Similarly, the urinary albumin excretion was reduced from 0.0051 to 0.0036 mg/mOsmol per liter. These data suggest that glomerular, rather than tubular, mechanisms account for the beneficial antiproteinuric effects of the ACE inhibitor.

See article at *J Pharmacol Exp Ther* 2015, **353**:299–306.

The Novel Action of the Prostaglandin I\(_2\) Mimetic ONO-1301 on Platelet Aggregation

ONO-1301 [(E)-5-[2-(1-phenyl-1-(3-pyridyl)methylidene)-aminooxy]ethyl]-7,8-dihydropyrimidine-1-yl]acylamide is a novel prostaglandin (PG) I\(_2\) mimic with inhibitory activity on thromboxane (TX) A\(_2\) synthase. ONO-1301 retains its inhibitory effect on platelet aggregation after repeated administration, while beraprost, a representative PGI\(_2\) agonist, loses its inhibitory effect after repeated administration. In addition, ONO-1301 inhibited arachidonic acid–induced TXA\(_2\) production in platelets lacking PGI\(_2\) receptor (IP). Beraprost could retain its antiplatelet effect after repeated administration in combination if it was dosed with ozagrel, a TXA\(_2\) synthase inhibitor. Therefore, it was hypothesized that chronic IP stimulation by beraprost induces an increase in TXA\(_2\) production, leading to reduction in the antiplatelet effect. As expected, repeated administration of beraprost increased the plasma and urinary levels of a TXA\(_2\) metabolite, while ONO-1301 did not. In addition, beraprost could retain the ability to inhibit platelet aggregation after repeated administration in mice lacking the TXA\(_2\) receptor TP.

See article at *J Pharmacol Exp Ther* 2015, **353**:269–278.

Simultaneous Inhibition of Fatty Acid Amide Hydrolase and Monoacylglycerol Lipase

Monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH) inhibitors exert preclinical effects indicative of therapeutic potential. In the present study, FAAH and MAGL inhibition was examined separately and together in a \(\Delta^9\)-tetrahydrocannabinol (\(\Delta^9\)-THC) discrimination assay predictive of subjective effects associated with cannabis use. The relative contribution of \(N\)-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) to those effects was also examined. \(\Delta^9\)-THC dose-dependently increased \(\Delta^9\)-THC appropriate responses, whereas FAAH or MAGL inhibitors administered alone did not substitute for the \(\Delta^9\)-THC discriminative stimulus. Nonselective FAAH/MAGL inhibitors fully substituted for \(\Delta^9\)-THC. Full substitution for the \(\Delta^9\)-THC discriminative stimulus occurred only when both 2-AG and AEA were significantly elevated, and the patterns of increased endocannabinoid content were similar among brain regions. The results suggest that increasing both endogenous 2-AG and AEA produces qualitatively unique effects that are not obtained from increasing either 2-AG or AEA separately.

See article at *J Pharmacol Exp Ther* 2015, **353**:261–268.