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Directly Observable Behavioral Effects of Lorcaserin in Rats

Lorcaserin is approved for treating obesity and its therapeutic effects are thought to result from agonist activity at serotonin (5-HT)2C receptors. The current study compared the behavioral effects of lorcaserin to the effects of other 5-HT receptor agonists in rats. The 5-HT2C receptor selective agonist mCPP (0.032 - 1.0 mg/kg) and lorcaserin induced yawning that was attenuated by the 5-HT2C receptor selective antagonist SB 242084. The 5-HT2A receptor selective agonist DOM (0.1-3.2 mg/kg) induced head twitching that was attenuated by the 5-HT2A receptor selective antagonist MDL 100907. In rats pretreated with SB 242084, lorcaserin also induced head twitching. At larger doses, lorcaserin produced forepaw treading that was attenuated by the 5-HT1A receptor selective antagonist WAY 100635. While the behavioral effects of lorcaserin in rats are consistent with 5-HT2C receptor agonist activity, these data suggest that, at larger doses, it also has agonist activity at 5-HT2A and possibly 5-HT1A receptors.

See article at *J Pharmacol Exp Ther* 2015 **355**:381-385.

Magnesium Modifies the Impact of Calcitriol Treatment In Chronic Kidney Disease

Chronic kidney disease (CKD) patients are commonly treated with vitamin D analogs, such as calcitriol. Recent epidemiological evidence revealed a significant interaction between vitamin D and magnesium, suggesting that increased magnesium improved mortality. The aim of the present study was to assess the mechanisms involved by determining whether magnesium combined with calcitriol treatments had an impact on vascular calcification (VC) in male Sprague-Dawley rats with adenine-induced CKD. Given alone, calcitriol increased the prevalence of VC; but when magnesium was given in combination, the severity of calcification was attenuated in the abdominal aorta, iliac and carotid arteries. The decreases in vascular calcium content were associated with an increase in vascular Mg. Calcitriol treatment alone significantly decreased TRPM7 protein whereas the combination treatment increased both the mRNA and protein expression. These findings suggest that modifying the adverse effect profile of calcitriol with Mg may be a plausible approach to benefiting CKD patients prescribed calcitriol.

See article at *J Pharmacol Exp Ther* 2015 **355**:451–462.

Administration of Carvedilol Protects Against Doxorubicin-Induced Cardiomyopathy

This study tested for benefits of early administration of carvedilol against doxorubicin-induced cardiomyopathy. After 35 days, the left-ventricular ejection fraction (LEVF) was significantly lower in the group administered doxorubicin without carvedilol compared to animals administered carvedilol along with the doxorubicin. The protein expressions of fibrotic (Smad3, TGF-β), apoptotic (BAX, cleaved caspase 3, PARP), DNA-damage (γ-H2AX), oxidative-stress (oxidized protein), mitochondrial-damage (cytosolic cytochrome-C), heart failure (BNP), hypertrophic (β-MHC) biomarkers of LV myocardium showed higher levels in the animals not treated with carvedilol. The protein expressions of anti-fibrotic (BMP-2, Smad1/5), α-MHC, and phosphorylated-Akt were increased in animals treated with only doxorubicin. Interestingly, in the present study doxorubicin-induced cardiotoxicity enhanced the generation of cardiac stem cells in myocardium. Of importance was that carvedilol therapy further enhanced this phenomenon of progenitor cell renewal.

See article at *J Pharmacol Exp Ther* 2015 **355**:516-525.

Minimal Anticipated Biological Effect Level of Anti-CD28 Receptor Antagonist

BMS-931699, a domain antibody (dAb) conjugated with 40 kDa branched polyethylene glycol, is a human anti-CD28 receptor antagonist under development. The minimal anticipated biological effect level (MABEL) was determined for by integrating all the available preclinical data. The relevance of the in vitro mixed lymphocyte reaction (MLR) assay to a whole blood CD28 receptor occupancy (RO) assessment, as well as the relationship between the CD28 RO and the inhibition of T-cell-dependent antibody response to keyhole limpet hemocyanin in vivo, was demonstrated through an integrated PK/PD analysis using antihCD28 dAb-001 (differing from BMS-931699 by two additional amino acids at the N-terminus) and a mouse surrogate. Based on this analysis, the EC10 value (0.32 nM) from the human MLR assay and the human plasma volume (0.04 L/kg) were employed to calculate the MABEL (0.01mg) in humans, with a CD28 RO predicted to be ≤10%. It was 2900-fold lower than the human equivalent dose derived from the no observed adverse effect level in monkeys dosed weekly for 5 weeks. The MABEL dose was successfully used as the first-in-human starting dose for BMS-931699.

See article at *J Pharmacol Exp Ther* 2015 **355**:506-515.

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