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Highlighted Papers

N-Methyl-D-Aspartate Channel Blocker–Like Discriminative Stimulus Effects of Nitrous Oxide Gas

Nitrous oxide (N_2O) gas is a widely used anesthetic adjunct that is also commonly abused. In this study, the authors explored the receptor systems responsible for producing the discriminative stimulus effects of N_2O. Mice were previously trained to discriminate exposure to N_2O versus oxygen in a two-lever food reinforced operant task. *N*-Methyl-D-aspartate (NMDA) receptor channel blockers [(+)-MK-801 {(5*S*,10*R*)-(1)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate} and memantine] partially mimicked the stimulus effects of N_2O. However, neither the competitive NMDA antagonist, CGS-1975 (*cis*-4-[phosphomethyl]-piperidine-2-carboxylic acid), nor the NMDA glycine-site antagonist, L701-324 [7-chloro-4-hydroxy-3-(3-phenoxy)phenyl-2(1*H*)-quinolinone], produced N_2O-like stimulus effects. A range of other receptor agonists and positive modulators also failed to produce N_2O-like effects. (+)-MK-801 significantly enhanced the discriminative stimulus effects of N_2O. The results of the present study support the hypothesis that the discriminative stimulus effects of N_2O are at least partially mediated by NMDA antagonist effects similar to those produced by channel blockers.

See article at *J Pharmacol Exp Ther* 2015, **352**:156–165.

Antidepressants and Antipsychotics That Inhibit *Aa*DOP2 as Potential Insecticides

The yellow fever mosquito, *Aedes aegypti*, vectors disease-causing agents that can lead to dengue and yellow fever. Current mosquito control programs are challenged by the emergence of insecticide-resistant mosquitos. One recently identified potential insecticide target is the *A. aegypti* D_1-like dopamine receptor, *Aa*DOP2. In this study, in vitro assays revealed *Aa*DOP2 antagonism by four distinct chemical scaffolds from tricyclic antidepressant or antipsychotic chemical classes, and elucidated several structure-activity relationships that contributed to enhanced potency, including lipophilicity, halide substitution on the tricyclic core, and conformational rigidity. Among the compounds investigated, asenapine, methiothepin, and *cis*-(*Z*)-flupenthixol displayed subnanomolar IC_{50} values and caused rapid toxicity to *A. aegypti* larvae and/or adults in vivo. There was a significant correlation between in vitro potency for *Aa*DOP2 antagonism and in vivo toxicity, suggesting viability of *Aa*DOP2 as an insecticidal target.

See article at *J Pharmacol Exp Ther* 2015, **352**:53–60.

Analgesic Properties of a GalR2–Receptor Preferring Galanin Analog

The anticonvulsant neuropeptide galanin is a potent regulator of neuronal excitability, and has a well established role in pain modulation, making it a potential target for novel therapies. The authors designed peripherally-acting galanin analogs that exhibit preferential binding towards GalR2 over GalR1 galanin receptors. For the present work, preclinical analgesic and safety studies were conducted with a monodisperse oligoethylene glycol (dPEG)–containing galanin analog, NAX 409-9 (previously reported as GalR2-$dPEG_{24}$). NAX 409-9 increased the paw withdrawal threshold to mechanical stimulation following partial sciatic nerve ligation in rats (2 mg/kg). Conversely, NAX 409-9 had no effect in the tail flick or hot plate assays, and did not negatively affect gastrointestinal motility, respiratory rate, or bleed time. These studies illustrate that this nonbrain-penetrating galanin analog reduces pain behaviors in several models, and does not produce some of the dose-limiting toxicities associated with other analgesics.

See article at *J Pharmacol Exp Ther* 2015, **352**:185–193.

Disposition of Methylthioninium Redox Forms Determines Efficacy in Alzheimer's Disease

Methylthioninium (MT) is a tau aggregation inhibitor with therapeutic potential in Alzheimer's disease (AD). MT exists in equilibrium between reduced [leucomethylthioninium (LMT)] and oxidized (MT^+) forms; as the chloride salt [methylthioninium chloride (MTC)], it is stabilized in its MT^+ form. While the results of a phase 2 study of MTC in 321 AD subjects identified a 138 mg MT/day dose as the minimum effective dose, the 228 mg MT/day dose lacked efficacy. The authors hypothesized that the lack of a dose response may reflect differences in redox processing of MT at different levels in the gut. The synthesis of a novel chemical entity, LMTX (providing LMT in a stable anhydrous crystalline form), enabled a systematic comparison of the pharmacokinetic properties of MTC and LMTX in preclinical and clinical studies. The quantity of MT released in water or gastric fluid within 60 minutes proved to be an important determinant of clinical efficacy. There was also a dose-dependent limitation in the ability to absorb MT in the presence of food when delivered as MTC.

See article at *J Pharmacol Exp Ther* 2015, **352**:110–118.