In Vivo CNS Receptor Occupancy & In vitro Receptor Autoradiography

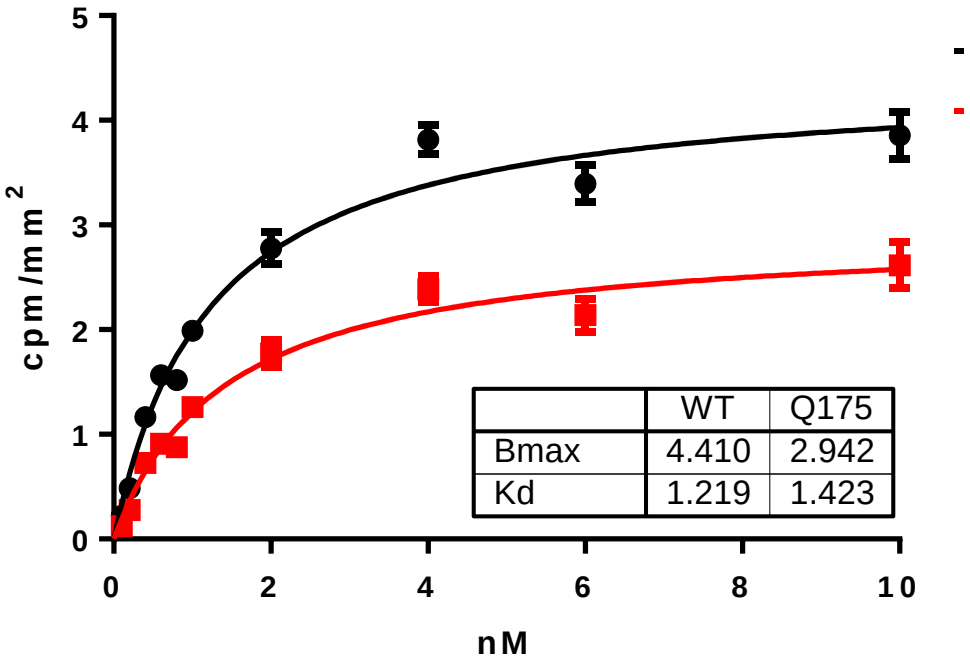
- **Beta-Imager**
  - **Can detect all beta emitting isotopes (^{3}H, ^{14}C, ^{32}P, ^{33}P, ^{35}S, ^{125}I)**
  - **Shortens the time needed for assessment of tritiated ligands imaging time from weeks to hours when comparing to film**
  - **Therefore is deal for:**
    - **Receptor occupancy studies**: an assay that could provide crucially important preclinical data for preclinical and clinical candidate selection, as a screening tool.
      - Ex Vivo: Only cold compound is administered (PO, IP, SC)
      - In vivo: Both radiolabeld (IV) and cold compound (PO, IP, SC) is administered
    - **Receptor autoradiography:** Determine the tissue distributions of target of interest. To obtain ED50, Ki, Kd, and Bmax values.

PsychoGenics

Redefining Drug Discovery Through Innovation

Quantitative Autoradiography

There Is A 33% Decrease in D2 Receptor Expression in 9 Month Old Heterozygous Q175KI Male Mice Model of HD



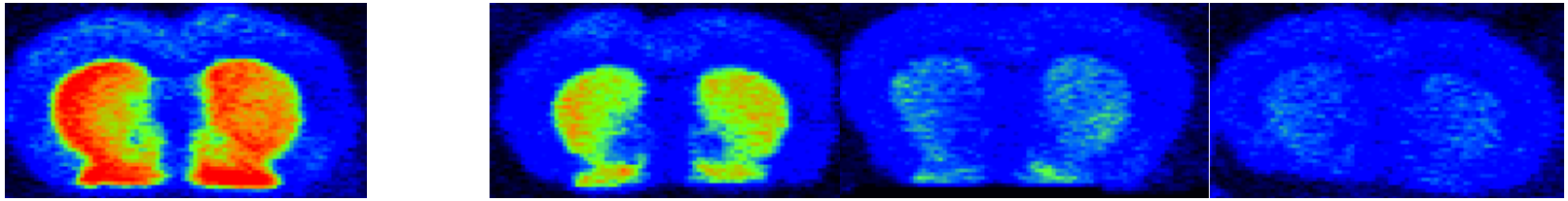
Dopamine D2 receptor saturation binding in the striatum of 9 month old z_Q175KI HET mice and their WT littermates. Calculated Bmax values for WT and z_Q175KI HET animals shows a loss in D2 receptor expression at 9 months of age (33%, **** $p < 0.0001$).

PsychoGenics

Redefining Drug Discovery Through Innovation

Ex Vivo Occupancy

Measurement of PDE10A inhibitor Target Occupancy



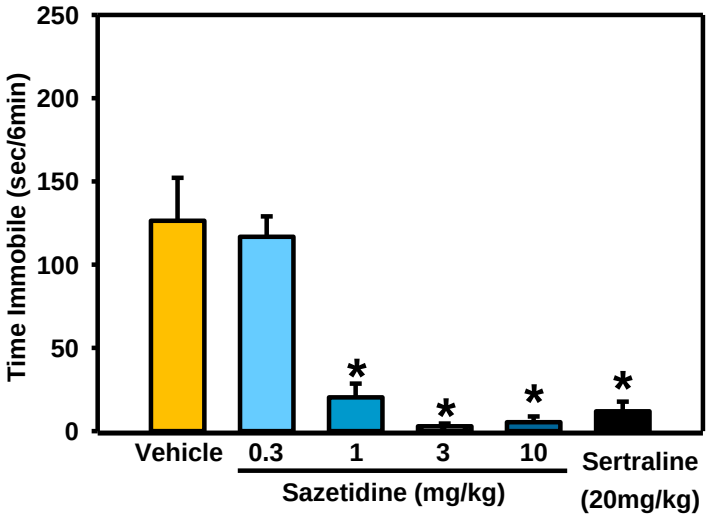
Vehicle | 1mg/kg | 3mg/kg | 10mg/kg

Ex vivo binding: PDE10 inhibitor, P.O., 1hr

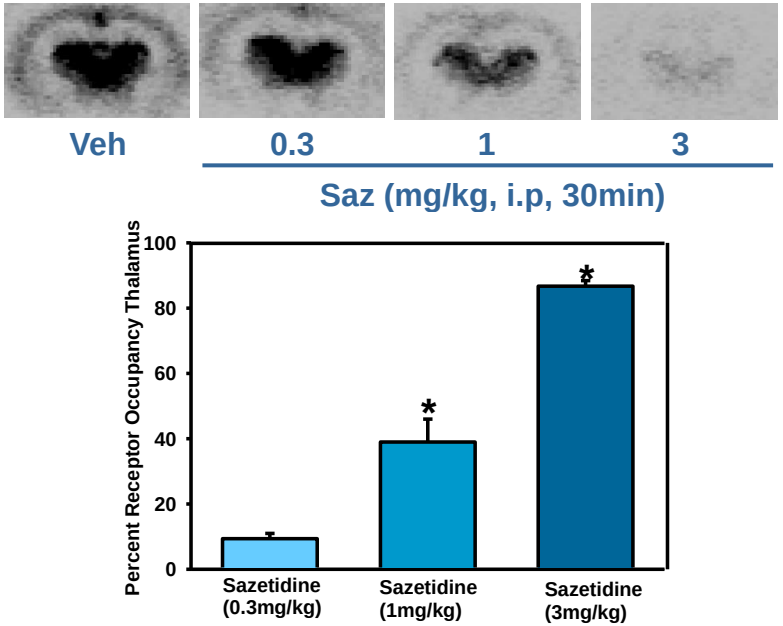
Ex Vivo RO/Efficacy Relationship

Sazetidine (α4β2 nAchR partial agonist) After ip Dosing in Mouse

Behavior: Forced Swim



Ex Vivo Binding



High correspondence between behaviorally active doses of sazetidine in the forced swim test and α4β2 nicotinic acetylcholine receptor (nAChR) occupancy in the brain. Specifically, sazetidine was inactive in the forced swim test at 0.3 mg/kg (i.p) and showed very low receptor occupancy at this dose (<10%). In contrast, doses of sazetidine (1 and 3 mg/kg, i.p.) that produced robust behavioral activity in the forced swim test, corresponded with high levels of occupancy at the α4β2 nAChRs (~40% and ~90% respectively).

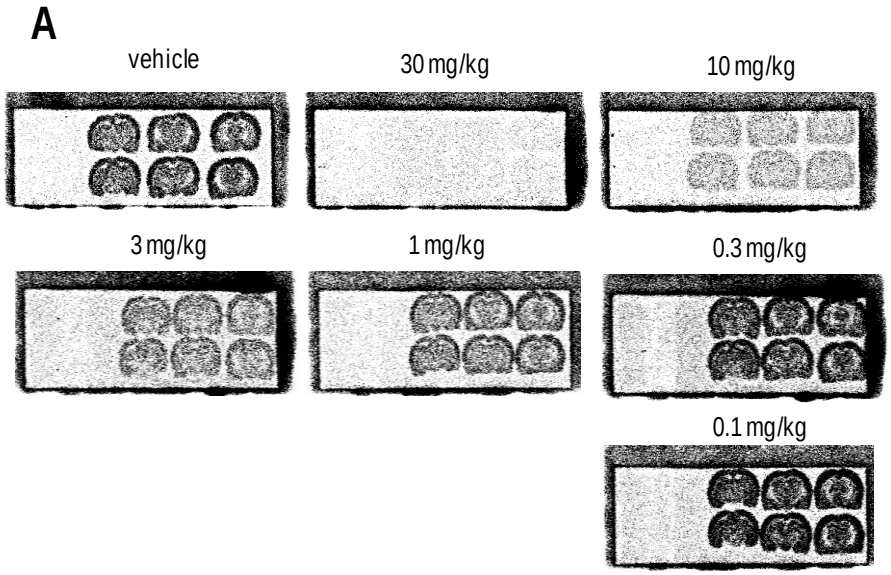
Caldarone et al, Psychopharmacology (Berl). 2011

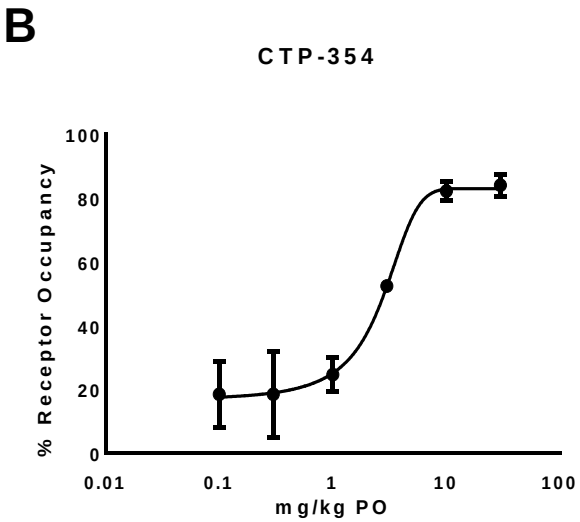
PsychoGenics

Redefining Drug Discovery Through Innovation

In vivo Occupancy

Brain Receptor Occupancy of CTP-354, a Selective Benzodiazepine Receptor ($GABA_A$) Modulator in Rats





Tracer: ^{3}H-Ro15-1788 (Flumazenil) administered by tail vein injection.

PsychoGenics

Redefining Drug Discovery Through Innovation

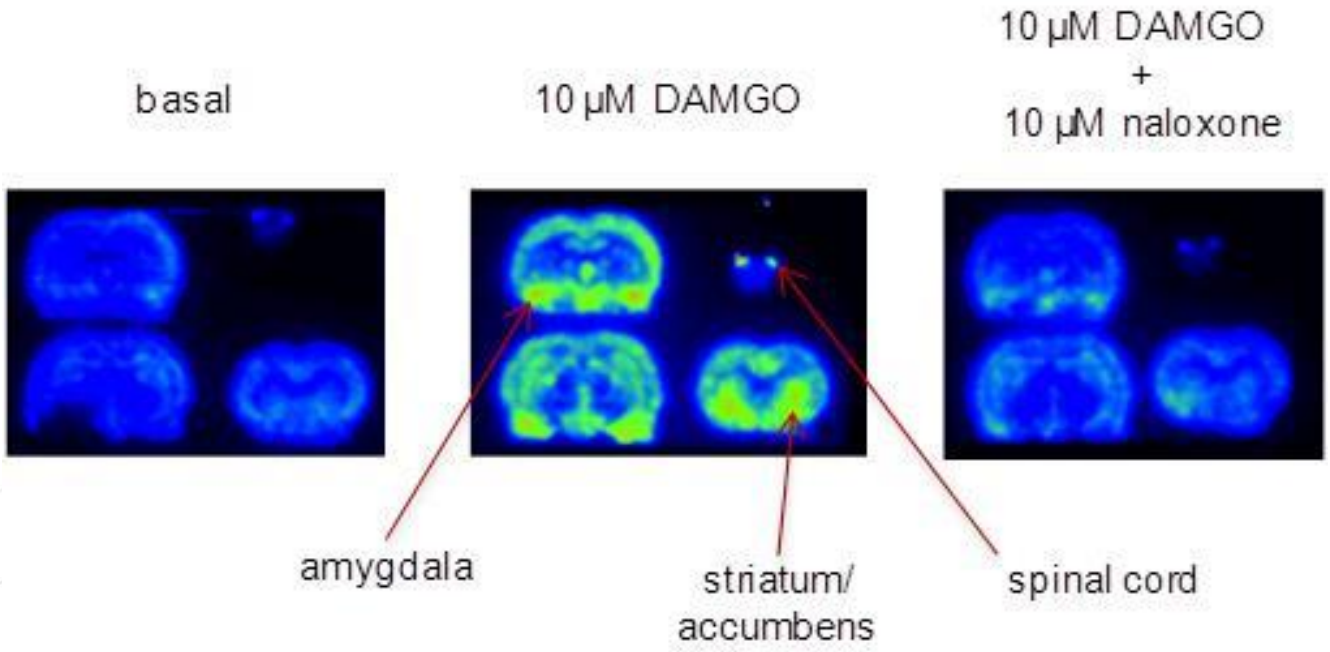
^{35}SGTPγS Binding

Assessment of Functional Activation of G_i/G_o-Coupled Receptors

μ-Opioid Receptors agonist DAMGO stimulates 35SGTPγS binding in the rat spinal cord, amygdala, and striatum/accumbens.

- The ^{35}SGTPγS assay allows for the assessment of functional activation of Gi/Go-coupled receptors by measuring bound ^{35}SGTPγS in brain sections using autoradiography.

- This assay is useful for investigating biased agonism in m-opioid receptors (MORs).



PsychoGenics

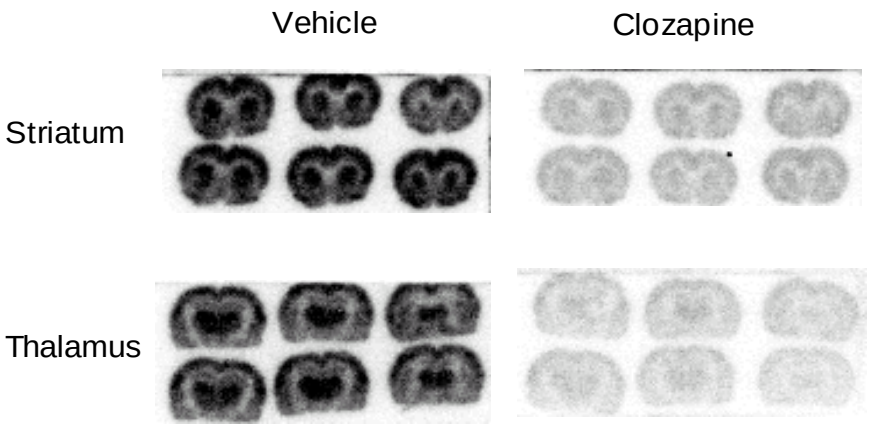
Redefining Drug Discovery Through Innovation

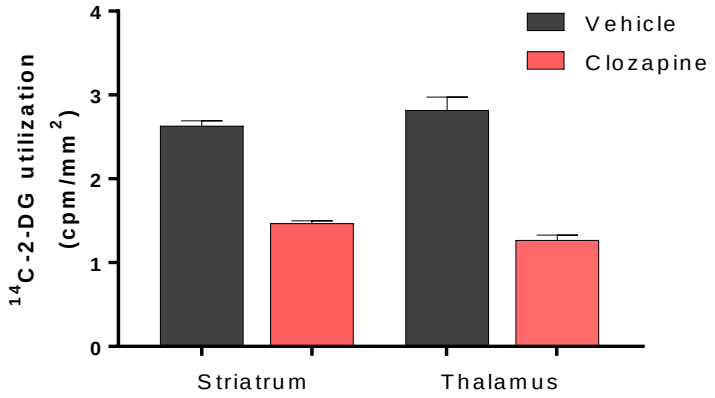
^{14}C-2-Deoxyglucose (^{14}C-2-DG) Autoradiography

Glucose Utilization as a Function of Neurogenic Activity

Measuring Glucose Consumption After Acute i.p. Administration of 20 mg/kg Clozapine Using ^{14}C-2-DG Autoradiography

- The ^{14}C-2-DG autoradiographic method can be used for measuring glucose utilization as a function of neurogenic activity.
- This assay is useful for identifying brain regions activated by specific drug agents, and therefore, can act as a surrogate for functional MRI.





Fifteen minutes after clozapine dosing, rats were i.v. tail vein injected with 25 µCi/kg of ^{14}C-2-DG. Rats were sacrificed 45 minutes post i.v. injection of ^{14}C-2-DG.