ABSTRACT

A body of research has demonstrated the effects of serotonin (5HT) systems on striatal dopamine (DA) release. Specifically, 5HT2A and 5HT2C serotonin receptors have been shown to exert opposite effects on striatal dopamine (for review see Boureau & Dayan, 2011). PET imaging in rats showed:

• 5HT2C antagonists increase striatal DA
• 5HT2A antagonists attenuate amphetamine-induced DA elevation in the striatum.

HYPOTHESIS: The effects of 5HT2C agonists will mirror those previously shown for 5HT2A antagonists, i.e., they will decrease striatal DA.

OBJECTIVE: To measure the effects of Vabicaserin (VABI), a 5HT2C agonist, on levels of endogenous DA and on amphetamine(AMPH)-induced DA release with PET.

METHODS

Tracer Administration: Bolus-injection
Scanner: Siemens FOCUS 220
Analysis: SRTM (Lammertsma, 1996)
Reference region: Cerebellum
Scan length: 11C-PHNO (2hrs); 18F-fallypride (3hrs)
Subjects: PHNO: 2 rhesus monkeys (M,F)
/fallypride: 3 rhesus monkeys (all M)

(expected) Primary Endpoints:
\[ \Delta B P_{\text{AMPH}} = 1 - \frac{B P_{\text{AMPH}}}{B P_{\text{Baseline}}} \]
\[ \Delta B P_{\text{AMPH}+\text{VABI}} = 1 - \frac{B P_{\text{AMPH}+\text{VABI}}}{B P_{\text{Baseline}}} \]

11C-PHNO design
(2 scans/day; randomized order)

Baseline
- SCAN: 120 minutes
Vabicaserin
- Vabicaserin: 1mg/kg infusion from 80 min before scan
  - SCAN: 120 minutes
Vobicaserin double dose
- Vobicaserin: 2mg/kg infusion from 80 min before scan
  - SCAN: 120 minutes
Amphetamine
- Amphetamine: 0.8 mg/kg (for bolus before scan)
  - SCAN: 120 minutes
Amphetamine + Vabicaserin
- Vabicaserin: 1mg/kg infusion from 80 min before scan
  - SCAN: 120 minutes

Regions of Interest: Caudate, Globus Pallidus, Nucleus Accumbens, Putamen, Substantia Nigra, Cerebellum (reference)

18F-fallypride design
(1 scan/day; randomized order)

Baseline
- SCAN: 180 minutes
Vabicaserin
- Vabicaserin: 1mg/kg infusion from 80 min before scan
  - SCAN: 180 minutes
Amphetamine
- Amphetamine: 0.8 mg/kg (for bolus before scan)
  - SCAN: 180 minutes
Amphetamine + Vabicaserin
- Vabicaserin: 1mg/kg infusion from 80 min before scan
  - SCAN: 180 minutes

Regions of Interest: Amygdala, Anterior Cingulate, Brainstem, Caudate, Cingulate, Frontal Cortex, Globus Pallidus, Hippocampus, Insula, Nucleus Accumbens, Occipital Cortex, Pons, Putamen, Substantia Nigra, Temporal Cortex, Thalamus, Cerebellum (reference)

DISCUSSION

In 2/2 monkeys, plasma levels of VABI below 200 ng/mL appeared to show a dose-dependent lowering of endogenous DA with higher plasma levels of VABI. (via 11C-PHNO)

In 1/2 monkeys, Vabicaserin attenuated an amphetamine-induced DA release measured with C11-PHNO.

Preliminary results in 3 monkeys suggest that lowering of endogenous DA and reduction in AMPH-induced DA release can be seen with 18F-fallypride.

Variability in plasma AMPH levels may necessitate a population approach akin to occupancy plots in drug occupancy studies. [AMPH-induced occupancy of D2 receptor plot] to show effects of Vabicaserin on AMPH-induced DA release.

Studies are ongoing to increase sample size and alternative analyses are being considered, such as an occupancy-curve-like approach to demonstrating VABI effects on DA release.

REFERENCES