Influence of positive allosteric modulation of the mGlu2-receptor on the behavioral responses in animal models of depression

Neuroscience Discovery

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ADAA – Chicago, March 28, 2014
Disclosure: Luc Ver Donck

- Employment: Janssen Pharmaceutica NV, a Johnson&Johnson company
- Stock shareholder: Johnson&Johnson
Glutamate

- Primary excitatory neurotransmitter in CNS (Riaza Bermudo-Soriano et al, 2012)

- Activates glutamate receptors (Kew & Kemp, 2005):
  - Ionotrophic: NMDA, AMPA
  - Metabotropic GPCRs (mGlu)

- mGlu receptors (Niswender & Conn, 2010):
  - 8 subtypes, 3 main groups
  - modulate glutamate tone and phasic release in a subtle manner
The metabotropic glutamate 2 receptor (mGlu2)

• Pre-synaptic group II receptor, Gi-coupled (Cartmell & Schoepp, 2000)

• Expression in prefrontal cortex, thalamus, striatum, hippocampus, amygdala (Wright et al, 2001, 2013; Lavreysen et al, 2013)

• mGlu2-activation reduces EPSPs: ↓ glutamatergic neurotransmission (Kew et al, 2001)
Excessive glutamatergic transmission

• Dysfunctional glutamatergic neurotransmission may be implicated in the pathophysiology of psychiatric illness.
  (Weinberger, 2007; Olney et al, 1999)

• Hypothesis: therapeutic efficacy by activation of group II mGlu receptors to normalise glutamatergic hyperexcitability.
  (Fell et al, 2011; Coyle, 2006; Johnson et al, 2005)
mGlu2 receptor activation

Tateyama et al, 2004
Havlackova et al, 2005
Rondard et al, 2006
Brock et al, 2007
mGlu2 receptor activation

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mGlu2 receptor modulation via allosteric site

Orthosteric agonist
- No subtype-selectivity
- Possibility of over-activation, desensitisation (tolerance)

PAM
- Structurally diverse and subtype-selective, wider chemical space
- Potentially better drug-like properties
- PAMs enhance transmission by endogenous transmitters and preserve temporal pattern of signaling (effective and safer approach?)

Tateyama et al, 2004
Havlackova et al, 2005
Rondard et al, 2006
Brock et al, 2007
JNJ-40411813, an mGlu2 Positive Allosteric Modulator (PAM)

- Positive efficacy cooperativity
- Minor intrinsic agonism

hmGlu2_CHOK1_glutamate_GTPγS; Mean ± SEM, n=17

Lavreysen et al, 2013
JNJ-40411813, a PAM at native mGlu2 receptors

- Acts as PAM at native mGlu2 receptors
- No effect in mGlu2 KO-mice

Brain Slices-[³⁵S]GTPγS autoradiography

Lavreysen et al, 2013
JNJ-40411813: target engagement at mGlu2

• **$5HT_{2A}$ occupancy due to rat-specific metabolite**

Lavreysen et al, 2013
Rodent tests of despair

• Acute tests:
  – Forced swim test
  – Tail suspension test

• (sub)-chronic test:
  – Dominant/submissive test
Forced swim test in mice

**Key measures:**
- Time Immobile
- Distance Moved

Test

-30 min

0-6 min
mGlu2-PAM does not reduce immobility time in forced swim test in mice

NMRI mice, n=10/group. 1w-ANOVA: * p<0.05 vs. vehicle
Treatment: 30 min pre-test
Tail suspension test in mice

Key measures:
- Time Immobile
- Distance Moved
mGlu2-PAM does not reduce immobility time in tail suspension test in mice

NMRI mice, n=15/group. 1w-ANOVA: * p<0.05 vs. vehicle
Treatment: 30 min pre-test
D/S : dominant/submissive test in rat

- Principle: competition for food between dominant-submissive pair of food deprived rats

D/S : dominant/submissive test in rat

• Model of human depression
  – Hypothesis: submissive behavior in social animals is related to human depression (Price, 1967)

• Like depressed humans, subordinate rats show: (Malatynska & Knapp, 2005)
  – Increased defensive behavior, weight loss
  – Major alterations in sleep, eating and active behaviors
D/S: dominant/submissive test in rat

- Reduction of Submissive Behavior Model:
  - Rodent model for depression
    - ‘depressed state’ is represented by the behavior of the submissive animal
  - Clinically effective antidepressants attenuate submissive behavior:
    - (des)imipramine, fluoxetine
  - No effect: neuroleptics, anxiolytics

Malatynska et al, 2002, 2007; Malatynska & Knapp, 2005
D/S: dominant/submissive test in rat

- Principle: competition for food between dominant-submissive pair of food deprived rats

**Dominant/submissive: study design**

<table>
<thead>
<tr>
<th>Week:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>Selection of D/S pairs (Δ &gt; 25%) (n=220)</td>
<td>Baseline drinking times (n=80)</td>
<td>Submitive: vehicle/drug Dominant: vehicle (n=10 pairs/group) + Daily D/S-test</td>
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- 23h food deprivation → 5-min D/S test → 1h food
- Treatments: 1h prior to test (*)

**Key measures:**
- Feeding score per rat
- Dominance level

D/S: Dominant/Submissive  
Male Sprague Dawley rats, age 8-10 w  
(*) : imipramine after test
Imipramine reverses submissive behaviour in rat

Mean ± SEM, n= 9 pairs; vehicle = 20% β-OH-cyclodextrin, imipramine: 10 mg/kg IP, QD week 3 through 5
***, ** P<0.01, 0.001 vs. dominance feeding score (student-t test)
JNJ-40411813 reverses submissive behaviour

Mean ± SEM, n= 9 pairs; JNJ-40411813: SC, QD week 3 through 5
*, **, *** P<0.05, 0.01, 0.001 vs. dominance feeding score (student-t test)

IVP-016-10
Imipramine and JNJ-40411813 reduce dominance levels in rat

Mean ± SEM, n= 9 pairs; vehicle (β-OH-cyclodextrin) or drugs, QD week 3 through 5
* , ** , *** P<0.05, 0.01, 0.001 vs dominance level of second week (2w-ANOVA followed by Bonferroni post tests)

IVP-016-10
Summary

• No effect of mGlu2-PAM in “acute” stress-related paradigms

• mGlu2-PAM reduces dominance level
  – Suggestive for antidepressant effect
Interpretation of drug effect in D/S test: potential caveats

• No mGlu2-PAM effect observed in (acute) depression paradigms forced swim and tail suspension tests
  – Different “state of mind” in sub-chronic D/S-test?

• Increased aggression in submissive animals?
  – mGlu2-PAM reduces aggressive behaviour in mice.

• Anxiolytic effects?
  – mGlu2-PAM had no effect in elevated plus maze, stress-induced hyperthermia, hole board.

• Change in food intake or appetite
  – mGlu2-PAM reduces food intake.
Conclusions

• The dominant-submissive model differentiates itself from the classical “acute” models of depression.
  – Animals are continuously exposed to psychosocial stressor (aggressor stress by the dominant partner)

• Subchronic stress conditions to submissive rat may affect:
  – Neurochemical signaling
  – Associated behaviour

• Continued treatment with an mGlu2-PAM under this subchronic stress condition:
  – Elicited antidepressant-like effects
  – Reflected by normalization of the behavioral responses
Acknowledgements

- Janssen Neuroscience Discovery and Early Development Teams

- Addex Therapeutics