Panic Disorder and Agoraphobia: Novel Glutamate Mechanisms and Therapeutic Approaches from Preclinical Models

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Collaborators

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Panic Disorder and Panic Attacks

- Panic disorder is characterized by recurrent “spontaneous” PANIC ATTACKS which are sudden onset of severe anxiety accompanied by multiple physical symptoms such as increases in respiration, heart rate, blood pressure.

- Panic Disorder begins in young adults; is a chronic illness; is a risk factor for suicide and many other cardiovascular and gastrointestinal illnesses.
Current Pharmacological Treatments for Panic Disorder are not Ideal

- The most commonly used treatments are antidepressants, but take a long time to work and often poorly tolerated.
- Benzodiazepines [e.g., Xanax (alprazolam)] are effective with rapid effects, but side effects such as sedation and dependence are common (Nutt et al., 2002; Baldwin et al., 2005; Bandelow et al., 2008; Cloos and Ferreira, 2009).

Therefore, there is a great need for rapidly effective anxiolytic agents without the typical benzodiazepine side effects.
Panic Attacks can be elicited with specific stimuli

- Although considered “spontaneous”, panic attacks can be reliably provoked in panic disorder subjects by normally innocuous interoceptive stimuli (e.g., intravenous 0.5M sodium lactate, 7% CO$_2$ inhalations or Cholecystokinin (CCK)).

This suggests that global neural pathways which modulate normal panic are perturbed in these subjects.
What is the ‘panic’ brain network?

Shekhar, et al., *TENS*, 2001
0.5M Sodium Lactate (i.v.)
An ordinarily mild Interoceptive stressor

Shekhar and Keim 1997, J Neuroscience
Johnson and Shekhar 2006, J Neuroscience
Sodium lactate elicits panic response only in panic-prone rats.

**Figure a.** Social Interaction Time

**Figure b.** Change in MAP

**Figure c.** Change in RR

**Figure d.** Change in HR

*Johnson et al., Neuropsychopharm 2008*
Systemic Infusion of SB334867, an Orexin 1 Receptor Antagonist, or Benzodiazepine Attenuates Lactate-induced Panic-like Responses in Panic-prone rats

Social interaction Box

Social Anxiety

Tachycardia

Locomotion “flight”

Pressor Response

Johnson et al., Nature Medicine 2010
Panic Symptoms are associated with elevated CSF ORX in suicide attempters

Johnson et al., Nature Medicine 2010
Panic and Phobias

- Agoraphobia is one of the most common consequences of panic disorder. It is a classic conditioned fear following an aversive experience.

- It affects over 50% of the PD subjects and results in the most severe disabling long-term consequences.

- What specific mechanisms predispose people with panic attacks to develop phobias so frequently?
Panic vulnerability enhances contextual conditioned fear and delays extinction.

Panic vulnerable rats show delayed extinction of conditioned fears

Shekhar, et al., *Unpublished*
Panic prone rats show reduced inhibition and increased excitation of amygdala

Molosh, et al., 2014 (submitted)
Gene Changes in Central Nucleus of Amygdala

\textbf{Gabrb2} – GABA(A) receptor, beta 2
\textbf{Grm2} – glutamate receptor, metabotropic 2

Molosh, et al., 2014 (Submitted)
Synaptic gene Changes in Panic-prone animals

Shekhar, et al., Unpublished
mGluR2 receptor positive allosteric modulator (PAM) as panic therapy

Shekhar et al. 2014 (Unpublished)
CONCLUSIONS

- Reduced MGlur2 receptors may be novel target implicated in panic attacks and agoraphobia

- MGlur2 receptor positive allosteric modulators (PAMs) may provide novel therapeutic approach for panic disorder
Questions?