A Negative Allosteric Modulator of the α7 Nicotinic Acetylcholine Receptor: A Potential Next Generation Treatment for Post Traumatic Stress Disorder

S.M. O'Connor, E.E. Doolin, C.J. Coles
Bionomics Limited, 31 Dalgleish Street, Thebarton SA 5031, Australia
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INTRODUCTION

PTSD is a complex disorder that develops in some people following exposure to severe trauma. Patients with PTSD display multiple symptoms in the clusters of intrusion, avoidance, arousal and reactivity and negative alterations of cognition and mood. Pharmacological treatment of PTSD is challenging and current medications such as selective serotonin reuptake inhibitors and benzodiazepines have limited effects in patients and multiple side effect issues.

BNC210 is a potent anxiolytic compound with antidepressant properties and few side effects. The novel mechanism of BNC210 is negative allosteric modulation of α7 nAChR which is activated when acetylcholine neurotransmission is increased in response to a variety of stressors. The receptor is widely distributed in the mammalian brain and is rich in areas such as the amygdala, pre-frontal cortex and hippocampus. The amygdala is involved in the assessment of threat-related stimuli and is necessary for the process of fear conditioning. Amygdala activation has been shown to be positively correlated with PTSD symptom severity and self-reported anxiety. In addition, functional neuro-imaging studies of PTSD have shown a positive correlation between amygdala and anterior cingulate cortex (ACC) responses in patients with more acute PTSD (Shin 2006, Brenner 2005).

SUMMARY

Studies in humans and animals indicate that the mechanism and pharmacology of BNC210 have therapeutic potential for the treatment of PTSD.

Acute doses of BNC210:

- Reduced number and intensity of panic symptom in animal and human models of panic
- Reduce anxiety and threat avoidance behavior in human and rodent models of anxiety
- Reverse amygdala hyperactivity induced by the emotional faces task in general anxiety disorder (GAD) patients
- Decrease the strong connection between the amygdala and anterior cingulate cortex in GAD patients

And, consistent with antidepressant treatment, the effects of BNC210 in animals are augmented with chronic administration for 14 days, giving a half log increase in potency.

BNC210 PTSD CLINICAL TRIAL OVERVIEW

BNC210 is being evaluated in a Phase II trial for PTSD in Australia and USA

DESIGN:
- Randomized, double-blind, parallel, placebo-controlled, multi-center study in Australia and USA; 192 subjects
- Placebo, BNC210 at 150 mg, 300 mg and 600 mg b.i.d.
- 12 week evaluation phase

PRIMARY OBJECTIVE:
- CAPS-5

SECONDARY OBJECTIVES:
- PTSD Checklist for DSM-5 (PCL-5)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Hamilton Anxiety Rating Scale (HAM-A)
- CANTAB Cognitive Assessment
- Clinical Global Impressions – Severity and Improvement Scale (CGI-S/CGI-I)
- Patient Global Impression – Severity and Improvement Scale (PGI-S/PGI-I)
- Assessment of Quality of Life (AQL-QoL)
- Social functioning: Sheehan Disability Scale (SDS)
- Sleep monitoring: Pittsburgh Sleep Quality Index (PSQI)

SAFETY:
- Safety and tolerability of BNC210
- Columbia Suicide Severity Rating Scale (C-SSRS)

AROUSAL AND REACTIVITY

In neuromaging studies, in GAD and PTSD patients, the emotional faces task activates the amygdala and connections between the anterior cingulate cortex and the amygdala are strengthened

In humans, BNC210 significantly reduced the degree and intensity of panic symptoms experienced during a CCK-4 induced panic attack

AVOIDANCE

BNC210 significantly reduced the intensity of defensive behavior in the Jostick Operated Runway Task (JORT) in Generalized Anxiety Disorder patients

DATA

**\( p = 0.048 \)**

**\( p = 0.041 \)**

**\( p = 0.008 \)**

**\( p = 0.007 \)**

**\( p = 0.033 \)**

**\( p = 0.027 \)**

**\( p = 0.021 \)**

**\( p = 0.0001 \)**

**\( p = 0.0001 \)**

During MRI, GAD patients “played a game” to evaluate drug effects on the intensity of avoidance behavior to a mild electric shock. Patients used a joystick to prevent the green dot being caught by the red dot. In half of the trials, a lightning symbol indicated that a mild shock would be delivered if the dots made contact. Compared to placebo treated patients, BNC210 (300 and 2000 mg; p.o.) significantly decreased the intensity of threat avoidance behavior; Lorazepam (1.5 mg; p.o.) also decreased the intensity of threat avoidance behavior but did not reach significance (Mean ± SEM; n = 21 GAD patients).

NEGATIVE ALTERATIONS IN COGNITION AND MOOD

BNC210 demonstrates activity in vitro and in vivo, consistent with antidepressant treatment

BNC210 enhanced neurite outgrowth in rat primary cortical neurons

Enhancement of neurite outgrowth and neuroprotection are features of antidepressants.

BNC210 significantly and dose-dependently enhanced neurite outgrowth (1-100 µM) compared to vehicle in rat primary cortical neurons. BDNF (50 ng/ml) also significantly enhanced neurite outgrowth compared to vehicle. **\( p<0.01 \)**, ***\( p<0.001 \)** denote significant differences to vehicle (Mean ± SEM; n=164-181 cells).

INTRUSION

In a contextual fear-conditioning extinction paradigm in C5BL/6J mice, BNC210 enhanced fear extinction while diazepam demonstrated an inhibitory effect

On Days 1 and 2 of extinction, mice treated with BNC210 (100 mg/kg) spent less time freezing in response to the conditioned stimulus (tone) compared to vehicle-treated mice. Conversely, diazepam treated mice (0.5 mg/kg) spent more time freezing on Days 1 and 2 compared to vehicle treated mice. *\( p<0.03 \), **\( p<0.0001 \)** denote significant differences to vehicle. (Mean ± SEM; n=12 mice).

In humans, BNC210 treatment reduced the emotional impact of a CCK-4 induced panic attack, showing enhanced recovery following an unpleasant emotional and physical experience

An emotional Visual Analogue Scale (eVAS) was used to subjectively assess emotional status at 5, 10, 20, 30 and 60 minutes following a CCK-4 induced panic attack. BNC210-treated subjects (2000 mg) were less distressed and recovered to baseline emotional status more rapidly than placebo-treated subjects (10’ versus 60’) (Mean ± SEM; n=15 healthy volunteers).

REFERENCES

2. Brenner et al., Fission emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual abuse; Neuropsychologia; 2005, 33: 761-69.