Pathophysiology of PTSD: Rethinking Drug Targets State of Science Summit 2017

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, Bremner 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:

- ✓ **Reduce 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 generalized anxiety disorder (GAD) patients**
- ✓ **Reduce 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 following 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 treatment phase

PRIMARY OBJECTIVE:

- CAPS-5

SECONDARY OBJECTIVES:

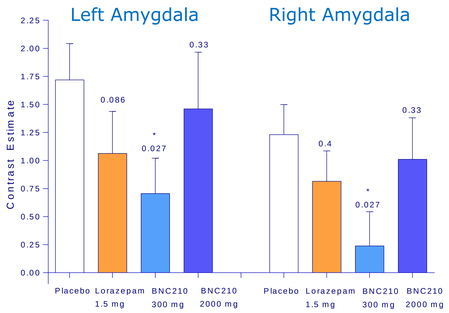
- PTSD Checklist for DSM-5 (PCL-5)
- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Hamilton Anxiety Rating Scale (HAM-A)
- CANTAB Cognitive Assessment
- Clinical Global Impressions – Severity and Improvement Scale (CGI-S/CGI-I)
- Patient Global Impression – Severity and Improvement Scale (PGI-S/PGI-I)
- Assessment of Quality of Life (AQoL-8D)
- Social functioning: Sheehan Disability Scale (SDS)
- Sleep monitoring: Pittsburgh Sleep Quality Index (PSQI)

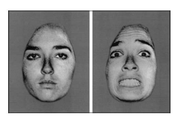
SAFETY:

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

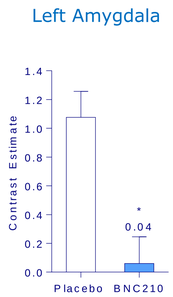
AROUSAL AND REACTIVITY

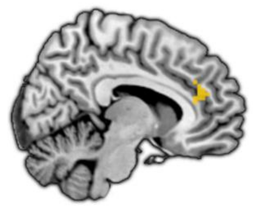
In neuroimaging studies, in GAD and PTSD patients, the emotional faces task activates the amygdala and connections between the anterior cingulate cortex and the amygdala are strengthened





(Ekman & Friesen 1975)





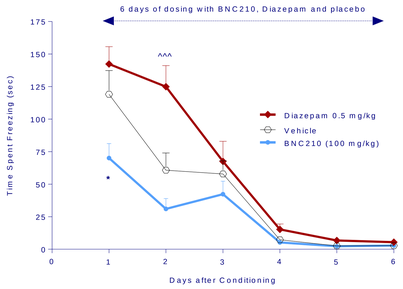
Anterior cingulate cortex

BNC210 treatment (300 mg; p.o.) significantly reduced left and right amygdala reactivity to fearful faces during fRMI compared to placebo treatment. Lorazepam (1.5 mg; p.o.) and BNC210 (2000 mg) also reduced left and right amygdala activity but did not reach significance (Mean ± SEM; n=21 GAD patients)

BNC210 (300 mg; p.o.) significantly reduced the connectivity between the left amygdala and anterior cingulate cortex in GAD patients while viewing fearful faces during fRMI.

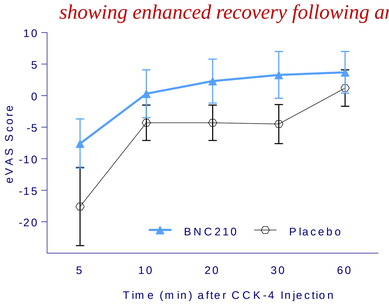
INTRUSION

In a contextual fear-conditioning extinction paradigm in C56BL6 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. *p0.03; ^^^p≤0.0001 denotes significant differences to vehicle. (Mean ± SEM; n=12 mice).

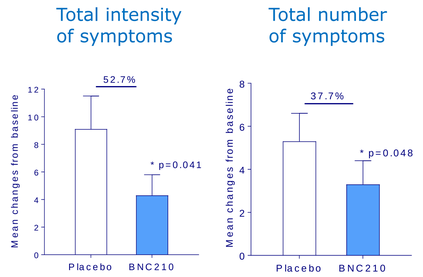
In humans, BNC210 treatment reduced the emotional impact of a CCK-4 induced panic attack, showing enhanced recovery following an unpleasant physical and emotional experience



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).

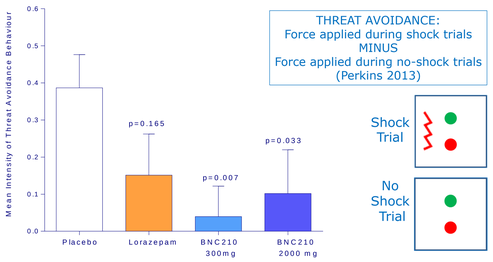
AVOIDANCE

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



The 18-item Panic Symptoms Scale (PSS) was used to evaluate the effect of BNC210 (2000 mg) versus placebo treatment. Data shown was measured at 10 minutes post CCK-4 injection (Mean ± SEM; n=15 healthy volunteers who panicked).

BNC210 significantly reduced the intensity of Defensive Behavior in the Joystick Operated Runway Task (JORT) in Generalized Anxiety Disorder patients

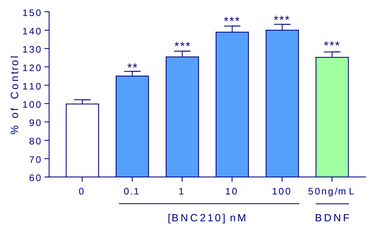


During fMRI, GAD patients "played a game" to evaluate drug effects on the intensity of avoidance behavior to a mild electric shock. Patients used a joystick to prevent the green dot being caught by the red dot. In half of the trials, a lightning symbol indicated that a mild shock would be delivered if 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

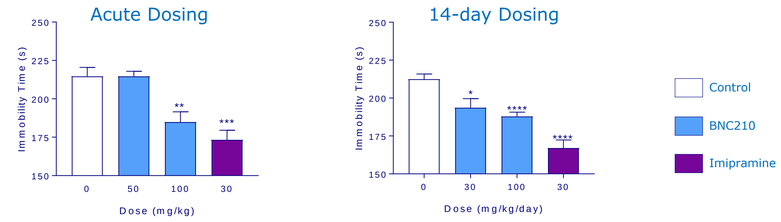
BNC210 demonstrates activity in vitro and in vivo, consistent with antidepressant treatment

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 nM) 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 denotes significant differences to vehicle (Mean ± SEM; n=164-181 cells).

BNC210 reduced immobility time in the rat forced swim test, an effect which was increased by chronic administration for 14 days



*p≤0.05; **p≤0.01; ***p≤0.001; ****p≤0.0001 Significantly different to vehicle treated rats (Mean ± SEM; n =10-12).

References

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