Evaluation of the Novel Anxiolytic BNC210 in a Rat Model of Cholecystokinin-Induced Panic

O'Connor S.[1], Huyard B.[2], Wagner S.[2], Kremmidiotis G.[1] and Andriambeloson E.[2]

1. Bionomics Limited, 31 Dalgleish Street, Thebarton S.A 5031, Australia.
2. Neurofit SAS, Boulevard Sébastien Brandt, Bioparc, Illkirch 67400, France.

Bionomics Limited

NEUROFIT PRECLINICAL RESEARCH

INTRODUCTION

BNC210 is a novel compound in development for the treatment of Generalized Anxiety Disorder (GAD) with co-morbid depression. It exhibits potent anxiolytic and antidepressant activity in preclinical animal models without displaying the side effects of currently marketed treatments for anxiety (benzodiazepines and SSRIs). BNC210 has a particularly strong anxiolytic effect in rodent models of physically induced stress (e.g., forced swim stress followed by Elevated Plus-maze (EPM)), which has led to its evaluation in a rodent model of pharmacologically induced stress.

Cholecystokinin (CCK) is a neurotransmitter, hormone and neuromodulator which binds to CCK_A and CCK_B receptors. Two centrally active peptides of CCK, the tetrapeptide CCK-4 and the unsulfated octapeptide CCK-8us, have a high affinity for CCK_B receptors which are distributed widely throughout the brain. The involvement of CCK in human anxiety is well documented and the administration of CCK_B receptor agonists such as CCK-4, provokes panic attacks in man and provides a model for assessing novel anxiolytic compounds in healthy volunteers. BNC210 has been evaluated in Phase I trials for safety, tolerability and food effect (See poster P.4.a.010).

AIMS & METHOD

AIMS: To investigate the potential of BNC210 to reverse the effects of pharmacological challenge by CCK_B agonists CCK-8us and CCK-4 and to compare the performance of BNC210 to the benzodiazepine, Diazepam, which is prescribed for the treatment of anxiety and panic disorder and is active in human models of CCK-4 challenge.

METHOD: The EPM was used to evaluate the anxiety state of rats treated with either single doses of BNC210, Diazepam, CCK-4 or CCK-8us; or with BNC210 or Diazepam in combination with the CCK peptides. BNC210 and Diazepam were administered *per os,* 1 hour prior to the implementation of the test. The CCK peptides were administered IP, 30 min prior to testing. Data was expressed as Time (spent on), and Entries (into), the open arms of the EPM. Devazepide, a CCK receptor antagonist with demonstrated preclinical anxiolytic activity in this model (Chopin and Briley, 1993), was used as a positive control. Statistical analysis was performed using the Unpaired T-test (Graph Pad PRISM Version 4.03).

RESULTS

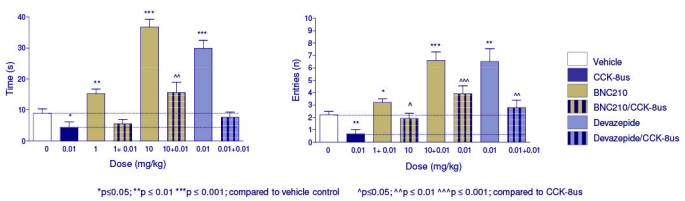

FIGURE 1: Administration of CCK-8us (0.01 mg/kg) produced an anxiogenic response in rats on the EPM as demonstrated by the significantly lower scores of CCK-treated rats, compared to vehicle-treated rats, on the Entries and Time parameters. BNC210 (1 and 10 mg/kg) was very effective at reversing the anxiogenic effects of CCK-8us and reached statistical significance for Time at 10 mg/kg, and for Entries at 1 and 10 mg/kg. The CCK receptor antagonist Devazepide significantly reversed the anxiogenic effects of CCK-8us on the Entries parameter. n=10 rats

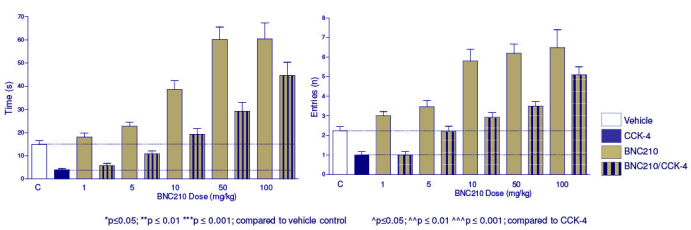

FIGURE 2:. CCK-4 is the peptide used in human CCK challenge studies. The ability of BNC210 to reverse CCK-4 (0.2 mg/kg) induced anxiety was studied in the rat EPM. BNC210 (1–100 mg/kg) fully reversed the anxiogenesis produced by CCK-4 in a dose dependent manner from ≥5 mg/kg. n=10-25 rats

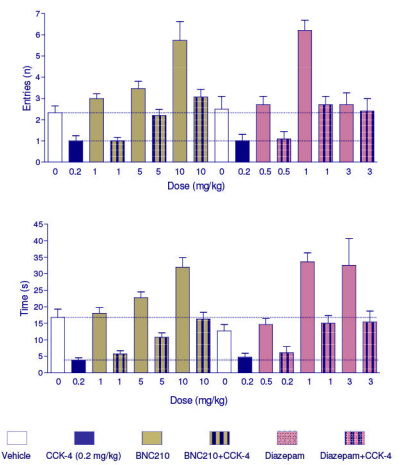

FIGURE 3: Diazepam is prescribed for anxiety and panic disorder and is active in human models of CCK-4 challenge. BNC210 (1, 5 and 10 mg/kg) and Diazepam (0.5, 1 and 3 mg/kg) were compared in the rat EPM for their ability to reverse CCK-4 (0.2 mg/kg) induced anxiety. BNC210 reversed the effect of CCK-4 at 5 and 10 mg/kg. Diazepam was effective at 1 mg/kg but the higher dose of 3 mg/kg produced clear signs of sedation. BNC210 demonstrated equivalent efficacy to Diazepam in this model, and a broad therapeutic window due to its lack of sedative side-effects. n=10-15 rats

DISCUSSION

The work presented here demonstrates that BNC210 reverses the anxiogenic effects of CCK peptides in rats. It is well documented that the administration of CCK_B receptor antagonists such as CCK-4, provoke panic attacks in man (Bradwejn, 1993). Benzodiazepines have demonstrated efficacy in both rat and human models of CCK challenge and the data presented in this poster shows that BNC210 is more effective than Diazepam in the rat model.

Based on these results, it is reasonable to suggest that BNC210 treatment may attenuate the panicogenic effects of CCK-4 in healthy volunteers and thus be of therapeutic benefit for panic disorders in addition to GAD. Measurements of BNC210 exposure in a recent human Phase I study has indicated that BNC210 plasma exposure is more than sufficient to warrant evaluation of BNC210 in a clinical study using the CCK-induced panic model in healthy volunteers.