1. THE ANXIGENIC EFFECT OF CCK-4 WAS REVERSED BY BNC210 IN RAT EPM

Anxiolytic activity and enhancement of fear extinction demonstrated by BNC210 in rodent models translates directly to the clinic in a CCK-challenge model of panic attack in healthy volunteers

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INTRODUCTION

BNC210 is a negative allosteric modulator of the u7 nicotinic acetylcholine receptor in development for the treatment of anxiety disorders.

Deficits in fear extinction are thought to contribute to the development of anxiety disorders. Fear condtioning is a behavioral paradigm used to assess memory associated with fear and emotion with the pairing of an environmental cue or conditioned stimulus (CS - tone) and an aversive unconditioned stimulus (US) such as a mild foot shock (2). This model was used in mice to explore whether BNC210 could enhance fear extinction and thus improve recovery from panic attack.

Cholecystokinin (CCK) is a neurotransmitter, hormone and neuromodulator which binds to CCK1 and CCK2 receptors. Administration of CCK-4 produces anxiety in rodents and panic attacks in man which provides a model for assessing novel anxiolytic compounds in healthy volunteers. Here it is shown that BNC210 activity in animal models translates to the clinic.

METHODS

ELEVATED PLUS MAZE (1)

BNC210 (1-100 mg/kg, p.o.) and Diazepam (0.5-3 mg/kg, p.o.) were administered to rats in single doses with and without CCK-4 (0.2 mg/kg) to assess the effect on CCK-4 induced anxiety. BNC210 and Diazepam were administered 1 hour prior to testing with CCK-4 administration (i.p.) 30 min prior to testing. Data was expressed as Entries (into) and Time (spent on) the open arms of the EPM. Statistical analysis was performed using the Unpaired T-test (Graph Pad Prism Version 6).

CONCEPTUAL FEAR CONDITIONING

A conditioned fear response (freezing) was acquired during the CS (tone) and US (shock) pairing. CS-US pairing session: C57BL6 mice were placed into an enclosure with an electrically grid bottom. A tonal cue was played (CS) which was followed by a mild foot shock (US). After a 120 sec inter-trial interval animals were presented with a second tonal cue-shock pairing (CS-US). Extinction was initiated 24 hours after the acquisition of fear response. CS only extinction session: mice were dosed daily for 6 days with either vehicle or BNC210 (p.o.) or Diazepam (p.o.) 1 hour prior to the first extinction session each day. On days 1-13 mice were exposed to 10 CS only presentations at intervals of 60 seconds. On days 4-7, 2 CS only presentations occurred. Time spent freezing was measured and used as an endpoint for strength of the CS-US association and the rate of fear extinction.

Comparisons of all treatment groups were conducted using two-way ANOVA followed by a Bonferroni’s post hoc test for multiple comparisons using Graph Pad Prism Version 6.

HUMAN MODEL OF CCK-4 INDUCED PANIC

Symptoms of CCK-4 induced panic attack in man were assessed on the Panic Symptoms Scale (PSS) (3, 4). Healthy male volunteers received a single oral dose of BNC210 (200mg) or vehicle over two consecutive periods one week apart. In each period the subjects received a single iv bolus injection of 50ug CCK-4 at T=7 hours (BNC210 TMAX). An emotional Visual Analogue Scale (eVAS) (5) was used to subjectively assess recovery to emotional stability at 5, 10, 20, 30 and 60 min following CCK-4 injection. Statistical analysis was performed using the Unpaired T-test (Graph Pad Prism Version 6).

RESULTS

1. THE ANXIGENIC EFFECT OF CCK-4 WAS REVERSED BY BNC210 IN RAT EPM

2. BNC210 SIGNIFICANTLY REDUCED PSS SCORES IN CCK-4 CHALLENGE IN MAN

3. BNC210 DECREASED THE TIME SPENT FREEZING IN A MOUSE MODEL OF CONTEXTUAL FEAR CONDITIONING EXTINCTION

4. BNC210 ENHANCED RECOVERY OF EMOTIONAL STABILITY FOLLOWING CCK-4 INDUCED PANIC ATTACK IN MAN

REFERENCE


CONCLUSIONS

The effects of BNC210 on panic symptoms following a CCK-induced panic attack in healthy volunteers, represent direct translation of pre-clinical EPM data to the clinic.

The effects of BNC210 on enhanced recovery of emotional stability following a CCK-induced panic attack in healthy volunteers, represent direct translation of rodent fear extinction data to the clinic.

The performance of Diazepam in the rodent CCK-4 and fear extinction models has also been translated to man. Benzodiazepines are an effective therapy for Panic Disorder with a limited dose range, and are contraindicated for PTSD due to impairment of fear extinction (6).

Recent clinical data in GAD patients (7) have demonstrated that BNC210 significantly dampens down amygdala activation in an emotional face task and produces significant reduction of simple avoidance responses.

Together these data support the evaluation of BNC210 in PTSD patients where high co-morbid anxiety (15-31%) (8) and deficits in fear extinction (9) are major symptoms.

Bionomics is currently enrolling PTSD patients in a Phase II trial.