The Novel Anxiolytic Compound BNC210 Reduces Stress on the Elevated Plus-maze in Pre-stressed Rats and Exhibits an Antidepressant Effect in the Rat Forced Swim Test

O’Connor S.1, Andriambeloson E.2, Huyard B.2, Wagner S.2, Sleebs B.3, Bui C.3, Street I.3 and Kremmidiotis G.1

1. Bionomics Limited, 31 Dalgielesh Street, Thebarton 5301, Australia. 2. Neurofit SAS, Bioparc, Parc d’ Innovation, Boulevard Sebastien Brant, Illkirch 67400, France. 3. Walter and Eliza Hall Institute Biotechnology Centre, Bundoora 3086, Australia

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Introduction

Generalised Anxiety Disorder (GAD) is a chronic, recurrent disease with a low rate of spontaneous remission that is characterised by excessive worry and interferes with the daily routine of those who suffer from it. The major pharmacologic agents currently used to manage patients with anxiety disorders include benzodiazepines, SSRI s and SNRIs; however, use of these agents is limited by a significant number of side-effects. Benzodiazepines produce sedation, motor defects, impairment of memory, dependence and tolerance. SSRIs and SNRIs have slow onset of action and side effects such as early agitation, sexual dysfunction and discontinuation syndrome. There is a clear medical need for fast-acting anxiolytic agents that lack the significant side-effects seen with current treatments.

We have identified the novel compound BNC210 and previously shown that it displays acute activity in several rodent models of anxiety (light dark box; mouse marble burying test; the elevated plus-maze and isolation induced vocalizations in guinea pig pups). Chronic administration of BNC210 does not result in development of tolerance to its anxiolytic effect. Most importantly, BNC210 does not cause sedation, even at very high dose levels, does not affect motor co-ordination and does not impair cognitive function. Furthermore, chronic administration of BNC210 does not cause any signs of abuse liability. BNC210 exhibits excellent oral bioavailability and plasma pharmacokinetics that are consistent with once a day dosing.

Materials & Methods

FORCED SWIM TEST. The forced swim test (FST) (Porsolt et al, 1978 Eur. J. Pharmacol. 47, 379- 392), is the most widely used paradigm for evaluation of the potential antidepressant effect of compounds. Antidepressants have the ability to increase escape motivated behaviour and to decrease immobility time. The test is performed for 5 minutes in a glass cylinder (35cm High; 24cm Diameter) containing water to a depth of 25 cm and maintained at a temperature of 25±1°C. Immobility time is measured.

Doses of BNC210 were administered to rats p.o., 60 min prior to the swim test. Imipramine was the comparator and was administered i.p., 30 minutes prior to the swim test.

FORCED SWIM STRESS. Experimental conditions employed in the forced swim test were used to generate a stress response in rats with the aim of evaluating the ability of BNC210 to moderate anxiety in pre-stressed animals. Rats were exposed to 90 seconds of swim stress 5 minutes prior to being evaluated in the elevated plus-maze test.

ELEVATED PLUS MAZE. The elevated plus maze (EPM) (Pellow et al, 1985 J. Neurosc. Meth 14:149-167) is based on the conflict between the innate tendencies of rodents to explore novel environments and to avoid open, bright lit areas. It is used to evaluate the relative anxiety status of rats. The ‘plus-shaped’ apparatus consists of four equal exploratory arms (45 × 10 cm) which are interconnected by a small platform (10 × 10 cm). Two arms are well lit and open and the other two are enclosed with 30 cm high walls and dimly lit. The apparatus is placed 66 cm above the floor. In this task the rat is placed in the centre of the maze from where it can walk down any of four runways. Rats prefer the closed arms but will venture out into the open arms. The amount of time spent in the open arms and the number entries into the open arms are recorded. “Anxious” rats will spend little time, and make very few entries, into the open arms. The apparatus is cleaned between each animal with 70% alcohol. Rats were exposed to 90 seconds of swim stress 5 minutes prior to being placed on the elevated plus-maze.

NON-PRECIPITATED WITHDRAWAL TEST. The aim of this assessment is to evaluate whether sudden cessation of drug treatment is associated with the occurrence of identifiable physical signs of withdrawal such as changes in body weight, food intake and body temperature. This method (Godfrey et al, 1993 Neuroreport 4:295-299) can be used to evaluate a wide variety of substances including those for which specific antagonists are not available. Rats received daily doses of BNC210, p.o for 14 consecutive days. Over the next 4-5 days following drug withdrawal, rats were measured for significant changes in food intake, body weight and body temperature.

Discussion & Conclusions

In addition to its effects on innate anxiety levels, BNC210 is effective in reducing stress-induced anxiety.

BNC210 exhibits antidepressant activity in the rat Forced Swim Test. The activity displayed by BNC210 was similar in magnitude to Imipramine. BNC210 antidepressant activity increased considerably following repeat administration for 14 days.

Withdrawal of BNC210 treatment following 14-day repeat dosing does not result in physical adverse events usually seen following withdrawal of opioids, benzodiazepines or SSRIs.

The activity profile seen with BNC210 in these preclinical tests expands its therapeutic potential to treatment of generalized anxiety disorder with co-morbid depression.

The safety and pharmacokinetics of BNC210 in healthy volunteers is currently being evaluated in a Phase I clinical trial.