The novel anxiolytic compound BNC210 is a negative allosteric modulator of the alpha 7 nicotinic acetylcholine receptor

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BNC210 under development for the treatment of anxiety disorders. Preclinical investigations showed BNC210 had anxiolytic efficacy similar to Diazepam without benzodiazepine-like side effects. This was further demonstrated in a Phase 1b study where, unlike Lorazepam, BNC210 did not cause cognitive impairment, sedation, coordination deficits or produce feelings associated with drugs of addiction. In rats, BNC210 was able to reverse the anxiety produced by CCK-8 and CCK-8 peptides as was subsequently tested in the CCK-4 induced panic model in healthy volunteers, and significantly reduced the number and intensity of panic symptoms, and ACTH levels. BNC210 has been evaluated in 148 healthy volunteers in 5 Phase 1 studies to date and is safe and well tolerated. In vitro studies have shown that BNC210 is an antagonist of the α7 nicotinic acetylcholine receptor (α7 nAChR). It inhibits rat and human α7 nACHR currents (in stably transfected cell lines) induced by acetylcholine, nicotine, choline and the α7 specific agonist PNU-282987, with IC50 values in the range of 1.2-3µM. BNC210 does not displace alpha-bungarotoxin binding and its inhibitory effects are not influenced by the concentration of acetylcholine used (EC20 or EC80), suggesting that the modulation is via an allosteric site.

METHODS

ELEVATED PLUS MAZE AND BASIC ANXIETY STATUS LEVEL

The elevated plus maze (EPM) (2) is based on the conflict between the innate tendency of rodents to explore novel environments and to avoid open, brightly lit areas and is used to evaluate relative anxiety status. The ‘plus-shaped’ apparatus consists of four exploratory arms (45 × 10 cm) which are interconnected by a small central open area (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 center of the maze from where it can walk down any of the four runways. Rats prefer the closed arms but will venture out into the open arms. The amount of time spent in open arms and the number of entries are recorded. Rats in “high anxiety status” spend less time and make fewer entries into the open arms compared to rats in “low anxiety status”. The anxiolytic effects of compounds are tested in rats with high basal anxiety levels. In contrast, the effect of anxiogenic compounds are investigated in rats with low basal anxiety levels. To reduce the level of basal anxiety in rats, they are handled and habituated to the experimenter on a daily basis for 7 days prior to the EPM experiments. Rats with high level of basal anxiety are not subject to the pre-handling process. BNC210 (p.o.) was dosed 1 hour prior to testing and PNU-282987 and MLA (both i.p.) were dosed 40 minutes prior to testing.

CONCLUSIONS

1. THE INHIBITORY EFFECTS OF BNC210 ARE NOT INFLUENCED BY ACETYLCHOLINE CONCENTRATION SUGGESTING THAT MODULATION IS VIA AN ALLOSTERIC SITE

BNC210 has been evaluated in 148 healthy volunteers in 5 Phase 1 studies to date and is safe and well tolerated. In vitro studies have shown that BNC210 is an antagonist of the α7 nicotinic acetylcholine receptor (α7 nAChR). It inhibits rat and human α7 nACHR currents (in stably transfected cell lines) induced by acetylcholine, nicotine, choline and the α7 specific agonist PNU-282987, with IC50 values in the range of 1.2-3µM. BNC210 does not displace alpha-bungarotoxin binding and its inhibitory effects are not influenced by the concentration of acetylcholine used (EC20 or EC80), suggesting that the modulation is via an allosteric site.

Although α7 nACHR antagonists have been associated with antidepressant activity, this target is novel for anxiolytics. We sought to demonstrate that in vivo anxiolytic activity of BNC210 is achieved through its negative allosteric modulation (NAM) of α7 nAChR. The α7 specific agonist PNU-282987 displays an anxiogenic effect in the rat Open Field (1). This compound was selected for its potential to block the anxiolytic activity of BNC210 in vivo. The rat elevated plus maze (EPM) was the model used to demonstrate the anxiogenic effect of PNU-282987, and then reversal of this effect by the α7 nAChR specific antagonists, methyllycaconitine (MLA, competitive) and BNC210 (non-competitive). These data support the hypothesis that the anxiolytic effect of BNC210 is achieved through negative allosteric modulation of α7 nAChR and indicates the involvement of this target in the modulation of anxiety.

REFERENCES