

## Neurokinin-1 receptor antagonists as novel antidepressants: trials and tribulations

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**Summary** Based upon animal experiments and early clinical trials, neurokinin-1 receptor antagonists showed promise as novel antidepressants. Subsequently, however, more extensive clinical trials did not reveal evidence of efficacy in depression. The development of novel antidepressants will require a better understanding of the neural basis of antidepressant action in humans.

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For the past 50 years the pharmacological treatment of depression has rested on the use of drugs that potentiate the activity of monoamines, particularly serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline. Both the tolerability and efficacy of current treatment is limited and there has been much effort to invent antidepressant agents with different modes of action and improved therapeutic profile. The difficulties confronting those engaged in this task are well illustrated by the clinical development of neurokinin-1 (NK<sub>1</sub>) receptor antagonists.

### SUBSTANCE P AND NK<sub>1</sub> RECEPTORS

Substance P is a neuropeptide that acts as a neurotransmitter or neuromodulator within both the central and peripheral nervous systems by preferentially binding to the NK<sub>1</sub> receptor. In many brain regions it acts as a co-transmitter with 'classical' monoamine neurotransmitters such as 5-HT and noradrenaline. A number of findings from animal studies are consistent with the notion that substance P and NK<sub>1</sub> receptors

might be implicated in the pathophysiology of depression (Kramer *et al*, 1998). First, NK<sub>1</sub> receptors are found in brain regions that are implicated in the regulation and expression of emotion, including the hippocampus, amygdala, prefrontal cortex and ventral striatum. Second, a variety of emotionally unpleasant stimuli, including foot-shock, pain, immobilisation and maternal separation increase substance P concentrations in limbic regions. Third, central administration of substance P produces behavioural and cardiovascular responses that resemble those seen following stressful stimuli. Fourth, there is significant overlap between 5-HT and noradrenaline pathways and substance P in limbic brain areas, and repeated administration of traditional antidepressants leads to decreased synthesis of substance P in certain brain regions. Fifth, mice in whom the NK<sub>1</sub> receptor has been knocked out are less anxious; for example, these mice exhibit greater exploration in the open field test. In addition, NK<sub>1</sub> receptor knockout mice are more active in the forced swim test, an effect similar to that produced by antidepressant treatment in wild-type mice (Santarelli *et al*, 2002).

There is little direct evidence in humans implicating substance P in depression, but substance P levels may be increased in cerebrospinal fluid in people with depression who are not on medication (Geraciotti *et al*, 2006). A post-mortem study of 12 depression patients, 6 of whom had died by suicide, found lowered NK<sub>1</sub> receptor numbers in the orbitofrontal cortex compared with controls (Stockmeier *et al*, 2002). This could be consistent with increased release of substance P.

### PRECLINICAL STUDIES OF NK<sub>1</sub> RECEPTOR ANTAGONISTS

Non-peptide antagonists for the NK<sub>1</sub> receptor were discovered about 15 years ago and

several highly specific ligands have been developed since. As expected, these drugs block the behavioural effects of centrally administered substance P as well as certain stress-related behaviours in which substance P has been implicated, for example, vocalisations by guinea pig pups separated from their mothers (Kramer *et al*, 1998).

NK<sub>1</sub> receptor antagonists are active in several animal models designed to detect anxiolytic and antidepressant effects. Some animal models of anxiety are based on unconditioned fear responses; these include the elevated plus maze or open field test, which measure aversion of rodents to novel, brightly lit environments. Similar models examine anxiety produced by social interaction with unfamiliar conspecifics or maternal separation. Other tests use conditioned anxiety responses where a stimulus (for example, a light) becomes aversive through being paired with a mild electric foot-shock. Conditioned anxiety models detect the effects of standard anxiolytics such as benzodiazepines. NK<sub>1</sub> receptor antagonists have been shown to have anxiolytic properties in the rodent elevated plus maze, rat social interaction test and fear-conditioning paradigms (see Ebner & Singewald, 2006).

Animal models are also used to detect potential antidepressant drugs. Some of these tests (for example, tail suspension of mice or the forced swim test in mice and rats) are used as assays which have proved sensitive to clinically established antidepressant drugs. Others, employing chronic environmental stressors, attempt to provide models of depression that have some face validity for the human disorder and which should therefore be sensitive to both established and novel antidepressant agents. For example, the chronic mild stress model in rats uses a variety of modestly unpleasant environmental manipulations, including changes of temperature and periods of food and water deprivation, to produce a decrease in the consumption of sucrose solution; this symptom is taken as an analogue of anhedonia and is reversed by chronic treatment with antidepressant drugs. Social stress and setbacks are known to be associated with depression in humans; therefore other animal models use stressful social manipulations to produce behavioural deficits (for example, decreased scent marking by tree shrews) that are sensitive to antidepressant administration. NK<sub>1</sub> receptor antagonists have antidepressant properties in the chronic mild stress and

social stress model as well as the forced swim and tail suspension tests (Ebner & Singewald, 2006).

## CLINICAL STUDIES OF NK<sub>1</sub> RECEPTOR ANTAGONISTS IN DEPRESSION

Kramer *et al* (1998) studied the effect of an NK<sub>1</sub> receptor antagonist, MK-869 (aprepitant), in a 6-week trial in about 200 people with major depression. Participants were randomly allocated under masked conditions to one of three treatments: aprepitant 300 mg daily, paroxetine 20 mg daily and placebo. Both aprepitant and paroxetine were significantly superior to placebo in lowering scores on the Hamilton Rating Scale for Depression (HRSD) and the Hamilton Rating Scale for Anxiety. Both active treatments were of equal efficacy but aprepitant was better tolerated than paroxetine, with increased levels of somnolence the only side-effect compared with placebo. In a further double-blind study of about 130 out-patients with melancholic depression, Kramer *et al* (2004) found that another NK<sub>1</sub> receptor antagonist (L-759274) also produced a significantly greater improvement in HRSD scores than placebo.

However, these compelling early findings were not supported by subsequent investigations. Keller *et al* (2006) reported results from five randomised, double-blind, controlled studies in over 2500 people with depression. They found that 8 weeks of treatment with aprepitant at doses of 80 mg and 160 mg showed no benefit over placebo. In contrast, paroxetine 20 mg daily, which was used as an active comparator in three of the five studies, was significantly better than placebo in each one. Positron emission tomography carried out at the same time indicated that both doses of aprepitant used in the trials would have produced high levels of central NK<sub>1</sub> receptor blockade with occupancy with the 160 mg dose regime being over 95% (Keller *et al*, 2006). Given together with dexamethasone and a 5-HT<sub>3</sub> receptor antagonist, aprepitant is licensed at daily doses of 80–125 mg for the prevention of chemotherapy-induced nausea and vomiting; this suggests that the doses employed in the clinical trials of people with depression would have been pharmacologically active.

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## CONCLUSIONS

More effective and better tolerated antidepressant medications are badly needed for the management of major depression; however, the development of the NK<sub>1</sub> receptor antagonists as antidepressants shows how formidable this task is. The NK<sub>1</sub> receptor antagonist aprepitant survived many hurdles at which candidate antidepressant drugs may fall. Aprepitant appears safe and well tolerated and has suitable oral pharmacokinetics for the treatment of depression. Two early clinical trials suggested efficacy.

A somewhat later, but major problem in the development of antidepressant drugs is the high frequency of failed trials in major depression; that is studies where both an active comparator as well as the compounds under investigation fail to show therapeutic benefits over placebo. However, this was not the case in the studies summarised by Keller *et al* (2006) in which the comparator drug paroxetine was indeed more effective than placebo. However, the problem seems to have been rather that the underlying concept of NK<sub>1</sub> receptor antagonism as an antidepressant mechanism may have been mistaken.

A major underlying problem in the development of new antidepressant drugs is the reliance on animal models to provide proof of concept because we lack valid animal models of depression. However, even with conditions such as head injury or neonatal respiratory distress syndrome, which can be more closely modelled in animal studies, clear concordance between beneficial effects of treatment in animals and patients is often lacking (Perel *et al*, 2007). We suggest that there is a need to develop new human models in which effects of potential antidepressants can be detected. This work requires a much better understanding of the interaction of antidepressant drugs with the neural circuitry involved in emotional regulation, work which modern methods of brain imaging is beginning to make possible (see Norbury *et al*, 2007). In addition, with appropriate

ethical safeguards it should be possible to carry out proof of concept studies of potential antidepressant agents in the most relevant participant groups; that is patients with depression or those at high risk (Bhagwagar *et al*, 2004).

The possible role of NK<sub>1</sub> receptor antagonists in the treatment of emotional disorders is still an area of active enquiry. The early clinical studies suggest that some people with depression may benefit, but identification of potential responders on clinical grounds alone seems unlikely to be successful. NK<sub>1</sub> receptors have pharmacological interactions with 5-HT pathways, hence it is conceivable that NK<sub>1</sub> receptor antagonists might augment the therapeutic effects of selective serotonin reuptake inhibitors in depressive and anxiety disorders (Ebner & Singewald, 2006). Finally it is probably easier to model anxiety than depression in animals, albeit normal anxiety responses to stressors rather than true pathological states. As noted above there is much evidence from animal studies that NK<sub>1</sub> receptor antagonists could have anxiolytic effects and there are now clinical data suggesting potential efficacy of another NK<sub>1</sub> receptor antagonist, GR205171, in patients with social phobia (Furmark *et al*, 2005). A number of other NK<sub>1</sub> receptor antagonists are still being investigated for their psychotropic potential.

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