

Peptides and Psychiatry, Part 3: Substance P and Serendipity: Novel Psychotropics Are a Possibility

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Issue: *Substance P and other neurokinins are, hypothetically, mediators of emotional distress in depression, anxiety, or schizophrenia. Preliminary indications that a substance P antagonist has antidepressant actions have triggered a race to discover novel antidepressants, anxiolytics, and antipsychotics that act by blocking substance P and other neurokinins.*

Science Versus Serendipity

Progress in psychopharmacology is largely the story of serendipitous clinical observations followed by controlled clinical trials. The most recent chapter in this story is the unexpected finding of antidepressant properties for a substance P antagonist.¹ Scientific rationale predicts that such agents should be blockers of neurogenic inflammation or pain, but clinical testing for these actions has been disappointing.²⁻⁴ That is, substance P is released locally during inflammatory responses that are neurogenically mediated. Also, substance P is released in the spinal cord in pain pathways. However, antagonists of substance P do not appear to

reduce neurogenic inflammation nor do they block pain in clinical trials. On the other hand, unexpected observations of improved mood in some studies of substance P antagonists being tested in pain and inflammation led to one as yet unreplicated report¹ of antidepressant actions comparable to the selective serotonin reuptake inhibitor paroxetine.

Breakthrough or Hype?

Hopes of a breakthrough antidepressant have been reported not only in the scientific literature but also in the financial press, where positive and negative rumors of how the neurokinin (NK) antagonists are faring in clinical trials can cause wild fluctuations in stock prices.^{5,6} Reasoned analysis does suggest that neurokinin antagonists might be novel psychotropic drugs. For example, substance P is located in brain areas associated with emotional behaviors, such as the hypothalamus and the amygdala and other areas of the limbic system.¹⁻⁴ Furthermore, substance P is also located near the cell bodies of dopaminergic and noradrenergic

neurons. Since dopamine and norepinephrine play key roles in depression and psychosis, and in the actions of antidepressant and antipsychotic drugs, it seems possible that substance P could modulate these neurotransmitter systems and thus affect emotional functioning. Indeed, preclinical studies are beginning to confirm that substance P plays a role in emotion¹ as well as in inflammation and pain.²⁻⁴

The Future

Currently, a number of companies are testing antagonists to substance P receptors (NK-1 antagonists) and to NK-B receptors (NK-3 antagonists) in both depression and schizophrenia. One published study¹ suggests an NK-1 antagonist causes less nausea and sexual dysfunction but more irritability than paroxetine, as well as comparable improvement in major depressive disorder.¹ Ongoing trials of various neurokinin antagonists are too early in testing to be conclusive, although recent reports of studies in the financial press⁶ suggest efficacy no better than placebo. However,

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Take-Home Points

- ◆ Substance P and other neurokinin (NK) neurotransmitters, such as NK-A and NK-B, may be released excessively during states of emotional distress. This is the conceptual foundation for a newly formulated theory of emotional distress, namely, the “neurokinin hypothesis of emotional dysfunction.”
- ◆ Selective antagonists for all 3 neurokinin receptors have been developed, and several are currently in clinical testing. These include blockers of substance P receptors (called NK-1 antagonists), blockers of NK-A receptors (called NK-2 antagonists), and blockers of NK-B receptors (called NK-3 antagonists).
- ◆ After years of disappointing results from clinical testing of antagonists to substance P receptors for their “rational” use in neurogenic inflammation or pain, one study¹ suggests that a substance P antagonist has unexpected antidepressant properties. The stage has been set to follow up this serendipitous finding through extensive clinical testing of a broad range of neurokinin antagonists as potential treatments for various emotional disorders ranging from depression to anxiety to psychosis.

these are early days in an exciting area of neuroscience. Neurokinin antagonists as novel psychotropics are still a provocative possibility.

Reminder

This is the last of a 3-part series on peptides and psychiatry. Part 1 appeared in January's BRAINSTORMS as a visual lesson on how neuropeptide neurotransmitters are synthesized, stored, and released in the central nervous system.⁷ Part 2 appeared in February's BRAINSTORMS and discussed 3 specific peptide neurotransmitters and their corresponding receptors, which belong to a special family of neuropeptides known as tachykinins/neurokinins.⁷ The 3 neurokinins discussed there were substance P, neurokinin A, and neurokinin B as well as their respective receptors, NK-1, NK-2, and NK-3. Here we have discussed how

antagonists to each of these 3 receptors are being rapidly developed and tested for their potential as novel psychotropic drugs. To get the best sense of the excitement that is sweeping through this area of psychopharmacology and to understand the potential breakthrough implications of substance P antagonists in psychiatry, it is important to grasp how peptide neurotransmitters differ from the better known monoamine neurotransmitters. It is also critical to understand key aspects of the biochemistry and pharmacology of 3 specific peptide neurotransmitters from the neurokinin family, especially substance P. Thus, after viewing this feature, the reader may wish to review parts 1 and 2 of this series^{7,8} and other reviews,²⁻⁴ especially if the psychopharmacology of neuropeptides and neurokinins is an unfamiliar topic.

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