**Mutagenesis and Knockout Models: NK1 and Substance P**

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**Abstract** Tachykinins play an important role as peptide modulators in the CNS. Based on the concentration and distribution of the peptides and their receptors, substance P (SP) and its cognate receptor neurokinin 1 (NK1R) seem to play a particularly important role in higher brain functions. They are expressed at high levels in the limbic system, which is the neural basis of emotional responses. Three different lines of evidence from physiological studies support such a role of SP in the regulation of emotionality: (1) stress is often associated with elevated level of SP in animals and humans; (2) systematic and local injections of SP influence anxiety levels in a dose-dependent and site-specific manner; (3) NK1 receptor antagonists show anxiolytic effects in different animal models of anxiety. Although these studies point to the NK1 receptor as a promising target for the pharmacotherapy of anxiety disorders, high affinity antagonists for the human receptors could not be studied in rats or mice due to species differences in the antagonist binding sites. However, studies on anxiety and depression-related behaviors have now been performed in mouse mutants deficient in NK1 receptor or SP and NKA. These genetic studies have shown that anxiety and depression-related phenotypes are profoundly affected by the tachykinin system. For example, NK1R-deficient mice seem to be less prone depression-related behaviors in models of depression, and one study also provided evidence for reduced anxiety levels. Mice deficient in SP and NKA behaved similarly as the NK1R knockouts. In animal models of anxiety they performed like wildtype mice treated with anxiolytic drugs. In behavioral paradigms related to depression they behaved like wildtype animals treated with antidepressants.
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summary, the genetic studies clearly show that the SP/NK1 system plays an important role in the modulation of emotional behaviors.

**Keywords** Substance P · Neurokinin 1 · Tachykinin · Anxiety · Knockout model

1 **Introduction**

Tachykinin neuropeptides can be found in many animal species from invertebrates to mammals. They have been implicated in a variety of physiological roles including immune, cardiovascular, gastrointestinal, pulmonary, and urogenital functions, as well as nociception (Severini et al. 2002). Much of the interest of the pharmaceutical industry in the tachykinin system has been stimulated by the proposed role of substance P (SP) in the facilitation of nociceptive signaling, and a considerable effort has been focused on the development of neurokinin (NK)1 receptor antagonists as an analgesic drug. However, although several antagonists have been developed and evaluated for the treatment of various pain conditions, none of these compounds showed much analgesic efficacy in clinical studies (Herbert et al. 2002).

Nevertheless, a potential use for these compounds came from the unexpected observation that tachykinin receptor antagonists seemed to be active in animal models of affective disorders. Indeed, a clinical study using the NK1 antagonist MK-869 confirmed these findings and demonstrated a very good efficacy of a tachykinin receptor antagonist for the treatment of depression (Kramer et al. 1998). The result of this first clinical study was recently confirmed in another clinical trial using a different NK1 antagonist, L-759274, in outpatients with major depressive disorder (Kramer et al. 2004).

Before we review some intriguing findings from the analysis of genetically altered animals, we will give a brief overview of the tachykinin system and summarize some pharmacological studies as they relate to its role in the regulation in emotional responses and, possibly, in the pathophysiology of affective disorders.

2 **An Overview of the Tachykinin System**

Von Euler and Gaddum described in 1931 a new substance from the alcoholic extract of equine brain and intestine that potently increased the rhythmic, spontaneous contractions of jejunum and produced hypotension relaxing the large arteries. They later called this compound substance P. The amino acid sequence of this peptide was established 40 years later by Leeman and cowork-