

Introduction

Pathophysiology of Depression: The Emerging Role of Substance P

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In recent years, antagonism of the substance P (SP)–neurokinin-1 (NK₁) receptor pathway has emerged as a novel approach to treatment of depression and associated anxiety. The following supplement, based on the symposium held on May 18, 2002, at the annual meeting of the Society of Biological Psychiatry in Philadelphia, Pennsylvania, provides an overview of our current understanding of the biology of the SP-NK₁ receptor pathway, its role in affective behavior, and clinical experience with SP (NK₁ receptor) antagonists (SPAs) in the management of depression.

In the first article, Patrick W. Mantyh, Ph.D., J.D. (University of Minnesota), describes the expression of SP and NK₁ receptors in the brain and spinal cord and briefly reviews the results of preliminary studies involving selective pharmacologic inactivation of NK₁ receptor–expressing neurons in various regions of the brain using cytotoxic SP-saporin (SAP) complexes. Numerous studies have demonstrated good colocalization of SP and NK₁ receptors in brain regions known to be involved in the regulation of affective behavior (e.g., amygdala, locus ceruleus, hypothalamus) and emesis (emetic nuclei). Additionally, colocalization of SP and NK₁ receptors in the spinal cord suggests that this system may also be involved in the control of nociception. An important feature of the SP-NK₁ receptor system is the fact that only a small proportion of neurons (5%–7%) in a given region express the NK₁ receptor, which is in contrast to broad expression of receptors for well-established neurotransmitters (e.g., serotonin, norepinephrine). On unstimulated neurons, NK₁ receptors are distributed in the plasma membrane of the cell body and dendrites, but, upon SP binding, they become rapidly internalized and are then quickly recycled to the surface. Acute stimulation of SP-containing neurons causes localized release of SP and activation of closely apposed NK₁ receptor–expressing neurons, whereas more intense or repeated stimulation results in SP diffusion farther away from the site of release and activation of greater numbers of neurons. Preliminary preclinical studies with SP-SAP complexes show that selective inactivation of NK₁ receptor–expressing neurons in amygdala results in anxiolytic effects, an observation that is consistent with the regulatory role of the SP-NK₁ receptor pathway in affective behavior.

The review by Luca Santarelli, M.D. (Columbia University), and colleagues discusses the effects of genetic or pharmacologic (using SPAs) inactivation of the NK₁ receptor in several types of behavioral assays. These studies have provided further evidence for the involvement of the SP-NK₁ receptor system in regulation of emotional responses and confirmed the therapeutic potential of SPAs in depression and associated anxiety. Additional studies have shown that behavioral effects of NK₁ receptor inactivation may involve increased serotonin-

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Supported by an unrestricted educational grant from Merck & Co., Inc., West Point, Pa. This supplement derives from a symposium held at the annual meeting of the Society of Biological Psychiatry, May 18, 2002, in Philadelphia, Pa.

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gic transmission in the dorsal raphe, an effect that correlates with down-regulation of inhibitory 5-hydroxytryptamine-1A (5-HT_{1A}) autoreceptors in this region. Subsequent experiments failed to demonstrate expression of NK₁ receptors on serotonergic neurons in the dorsal raphe and suggested that stimulation of serotonergic neurotransmission may be indirect. This concept was supported by the finding that the stimulatory effect of NK₁ receptor blockade/deletion on firing of serotonergic neurons in the dorsal raphe is completely abolished by pharmacologic ablation of noradrenergic neurons in the locus ceruleus, which have been shown to express NK₁ receptors. Therefore, the antidepressant and anxiolytic activity of SPAs may be mediated, at least in part, by their effect on noradrenergic/serotonergic neurotransmission.

© Richard Hargreaves, Ph.D. (Merck Research Laboratories), discusses the role of positron emission tomography (PET) imaging for dose optimization in studies with SPAs. PET is the only technique that allows in vivo monitoring of receptor occupancy in the central nervous system, but its role in clinical development of SPAs has so far been limited by the absence of suitable tracers. More recently, [¹⁸F]SPA-RQ has been developed as a brain-penetrant, NK₁ receptor-specific PET tracer that allows prolonged imaging time. Initial experiments with [¹⁸F]SPA-RQ demonstrated good colocalization with an autoradiographic [¹²⁵I]SP probe, paving the way for studies designed to examine the relationship between dose, NK₁ receptor occupancy, and clinical efficacy. Doses of SPA aprepitant (MK-0869) that showed significant clinical efficacy in the treatment of depression and chemotherapy-induced nausea and vomiting were found to provide > 90% NK₁ receptor occupancy, whereas < 90% NK₁ receptor occupancy was consistently observed with clinically less effective doses. These findings indicate that the goal of future dose-finding studies with SPAs should be to identify a dose that consistently provides >90% NK₁ receptor occupancy.

In the final article, K. Ranga R. Krishnan, M.B., Ch.B. (Duke University), reviews clinical experience with SPAs in treatment of depression. A phase 2 trial in patients with major depression showed antidepressant and anxiolytic effects of aprepitant that were quantitatively comparable to those seen with the selective serotonin reuptake inhibitor (SSRI) paroxetine and significantly greater than those reported with placebo. The beneficial effects of aprepitant in this study were accompanied by a favorable tolerability profile, most notably a significantly lower rate of sexual dysfunction than with paroxetine. These results established a proof of concept that SPAs may be clinically useful antidepressants. In a subsequent dose-finding study, neither aprepitant nor the SSRI fluoxetine was more effective than placebo. Lack of efficacy with a positive control (fluoxetine) in this study is characteristic of trials with all antidepressants (50% of which are negative) and indicates that no clinically relevant inferences about the efficacy of SPAs can be made on the basis of this study. Positive results seen in the phase 2 trial with aprepitant were recently replicated with a structurally different SPA, which is known as compound A, thereby further validating the potential therapeutic utility of this class of agents. Ongoing phase 3 trials with aprepitant will be instrumental in establishing the role of SPAs in the modern treatment of depression.