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Decreased cerebrospinal fluid concentrations of substance P in treatment-resistant depression and lack of alteration after acute adjunct vagus nerve stimulation therapy ☆

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Abstract

Recent preclinical and clinical research has demonstrated that the neuropeptide substance P (SP) plays a role in the central nervous system (CNS) response to stress, and perhaps in the etiology of major depression and/or anxiety disorders. The nature of this role, however, is poorly understood. A limited body of evidence suggests that in medication-free depressed patients, cerebrospinal fluid (CSF) concentrations of SP may be *elevated* relative to healthy controls. Two studies have shown that antidepressant treatment does not significantly change CSF concentrations of SP. Using standard lumbar puncture techniques, baseline CSF samples were obtained from 19 medication-free healthy controls and 19 medicated patients with treatment-resistant depression (TRD). Mean CSF SP concentration was significantly *lower* in TRD patients on psychotropic medications than in the group of healthy subjects. After 10–12 weeks of treatment with adjunct vagus nerve stimulation (VNS), CSF SP concentrations were not significantly changed. Low CSF SP may reflect a biological marker of the subtype of severe and chronic depression that is resistant to standard therapies.

Keywords: Substance P; Treatment-resistant depression; Cerebrospinal fluid; Vagus nerve stimulation

1. Introduction

Substance P (SP), an undecapeptide, was first discovered in crude form in 1931 by von Euler and Gaddum (von Euler and Gaddum, 1931), but its study was limited until its isolation by Leeman and colleagues

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in 1971 (Hokfelt et al., 2001). SP is found heterogeneously distributed in both the CNS and the peripheral nervous system (PNS). In the periphery, SP is located in the primary sensory neurons as well as in neurons within the gastrointestinal tract (Pernow, 1953).

SP belongs to the tachykinin family, which also includes neurokinin A and neurokinin B. Tachykinins originate from the preprotachykinin I (PPT-I) and preprotachykinin II (PPT-II) genes (Stout et al., 2001). Upon its release, SP binds to a family of neurokinin (NK) receptors, preferentially acting on the metabotropic NK1 receptor (Harrison and Geppetti, 2001).

Preclinical and clinical studies have suggested a potential antidepressant and anxiolytic effect of NK1 receptor antagonism (De Felipe et al., 1998; Bondy et al., 2003). For this reason, considerable attention has been given to the pharmacological development of SP antagonists (McLean, 2005). The rationale for this investment is multifold. One key set of preclinical research findings indicate that SP is released in response to stressful stimuli (Culman and Unger, 1995; Ebner et al., 2004). Further, SP-mediated activation of the NK1 receptor produces behavioral changes suggestive of "emotion modulation" in experimental animals (Elliott, 1988; Aguiar and Brandao, 1996; Teixeira et al., 1996). A second line of evidence supporting a role for SP in depression comes from data demonstrating that SP is co-localized within serotonergic and noradrenergic pathways (Santarelli and Saxe, 2003), and is found in regions that are involved in the regulation of mood and emotion, such as the amygdala, raphe nuclei, locus coeruleus, hypothalamus (Arai and Emson, 1986), limbic areas (Mantyh et al., 1984) and periaqueductal grey (Aguiar and Brandao, 1996). Thirdly, a growing body of results from preclinical and clinical investigations suggests that SP and the NK1 receptor are intimately linked with a diverse array of biological markers and neurotransmitter system abnormalities that have traditionally been associated with mood and anxiety disorders (Commons et al., 2003; Hwang et al., 2005). For example, behavioral and physiological effects produced by genetic or pharmacologic inactivation of the NK1 receptor in laboratory animals suggest anxiolytic- and antidepressant-like effects of SP antagonists (De Felipe et al., 1998; Ebner et al., 2004), which may be partially mediated by the alteration of neurofilaments and synaptic remodeling (Guest et al., 2004). NK1 antagonists have also been shown to increase the firing rate of serotonergic (Haddjeri and Blier, 2001; Santarelli et al., 2001), noradrenergic (Millan et al., 2001), and dopaminergic (Lejeune et al., 2002) neurons. Finally, SP circuits have long been implicated in nocioception, and recently in controlled studies the comorbidity of major depression and somatic pain (e.g., back pain, headache, abdominal pain, pelvic pain) has been unequivocally demonstrated (Ohayon and Schatzberg, 2003; Ohayon, 2004).

The measurement of CSF SP in humans has been a relatively neglected area. Rimon and colleagues (Rimon et al., 1984) reported that depressed patients had a fourfold increase in basal CSF SP-like immunoreactivity relative to patients with schizophrenia and healthy controls. However, two research groups (Berrettini et al., 1985; Deuschle et al., 2005) did not replicate this result. Our group recently reported elevated basal CSF SP concentrations in medication-free patients with major depressive disorder (MDD) relative to healthy control subjects (Geracioti et al., 2006). In the same report we also described elevated basal CSF SP in a group of medication-free adults with post-traumatic stress disorder (PTSD) and dynamic changes in CSF SP concentrations in response to acute psychological stress during serial sampling of CSF via indwelling lumbar intrathecal catheter.

Several groups have examined the effects of antidepressant treatment on concentrations of SP. In rodents, chronic administration of mianserin or one of several tricyclic antidepressants reduced SP content in the striatum, substantia nigra, and amygdala (Shirayama et al., 1996). However, in a study of humans, Deuschle et al. (2005) reported that pharmacological treatment of depressed patients with paroxetine or amitriptyline did not significantly alter CSF or plasma SP concentrations. Similarly, Martensson et al. (1989) found that successful treatment of depression with fluoxetine did not alter CSF SP levels. Both of those studies were limited by small numbers of subjects ($n=9$ and $n=11$, respectively). Two groups have described a relationship between clinical outcomes and serum SP concentrations. Bondy et al. (2003) noted a significant correlation between depressive symptoms scores and serum SP levels following antidepressant treatment. Patients who demonstrated a decrease from high baseline serum SP concentrations with treatment were more likely to experience a positive clinical response than those patients whose serum SP concentrations increased from their relatively low baseline values (Bondy et al., 2003). Lieb et al. (2004) also reported that antidepressant responders were characterized by high baseline serum SP concentrations that declined significantly with pharmacotherapy. Deuschle et al. (2005) did not confirm a difference in serum SP concentrations between antidepressant responders and nonresponders. It should be noted, however, that there are no data to suggest that serum SP concentrations reflect relevant CNS concentrations of the peptide (Landgraf et al., 1983; Freed et al., 2002).