

Serotonin hypothesis of winter depression: behavioral and neuroendocrine effects of the 5-HT_{1A} receptor partial agonist ipsapirone in patients with seasonal affective disorder and healthy control subjects

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Abstract

Winter depressions in seasonal affective disorder (SAD) are associated with central serotonergic (5-HT) dysfunction. SAD patients demonstrate rather specific, state-dependent, abnormal increases in ‘activation-euphoria’ ratings following intravenous infusion of the 5-HT receptor agonist meta-chlorophenylpiperazine (*m*-CPP). Several studies are also consistent with abnormal serotonergic regulation of the hypothalamic–pituitary–adrenal (HPA) axis in SAD. Here, we investigated the effects of the 5-HT_{1A} receptor partial agonist ipsapirone, which produces behavioral effects and HPA-axis activation, to further characterize the 5-HT receptor subtype-specificity of these disturbances in SAD. Eighteen SAD patients and 18 control subjects completed two drug challenges (ipsapirone 0.3 mg/kg and placebo) separated by 3–5 days in randomized order. We measured behavioral responses with the NIMH self-rating scale, and plasma ACTH, cortisol, and prolactin concentrations. Compared with placebo, ipsapirone was associated with significant increases in self-rated ‘functional deficit’ and ‘altered self-reality’, and in each of the hormones. There were no differences between groups on any measures. The level of depression in SAD patients was inversely correlated with their ipsapirone-induced cortisol responses. There were significant drug × order effects on baseline ‘anxiety’ scores, ACTH and cortisol concentrations, such that subjects were significantly more stressed (higher

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'anxiety', ACTH and cortisol) prior to their first challenge compared with their second. In conclusion, post-synaptic 5-HT_{1A} receptors appear to function normally in SAD. The previously observed *m*-CPP-induced behavioral abnormality may be mediated by either 5-HT_{2C} or 5-HT₇ receptors. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

In its original formulation, the serotonin (5-HT) hypothesis of seasonal affective disorder (SAD) (Rosenthal et al., 1984) stated that in winter, the decreased amount of sunlight leads to a deficiency of central serotonergic transmission and the development of clinical depression in patients with SAD. This hypothesis was based, in part, on the following observations. First, many of the symptoms of winter depression (e.g. hypersomnia and hyperphagia) were known to be regulated by hypothalamic 5-HT (Jouvet, 1969; Fernstrom and Wurtman, 1971). Second, hypothalamic 5-HT content had been shown to vary seasonally in post-mortem analyses of brains of healthy volunteers, with troughs in the winter (Carlsson et al., 1980). Third, seasonal rhythms had been reported in several peripheral indices of 5-HT metabolism [e.g. cerebrospinal fluid 5-hydroxyindoleacetic acid and platelet 5-HT uptake (Wirz-Justice and Richter, 1979; Swade and Copen, 1980)] which were thought to reflect similar seasonal rhythms in central 5-HT metabolism. Thus, patients with SAD were thought to be abnormally vulnerable to the decreases in hypothalamic 5-HT that normally occur during the winter (Rosenthal et al., 1995; Kasper et al., 1996) — a hypothesis that attracted considerable experimental support from investigations in both humans and animals (Rosenthal and Blehar, 1989).

Consistent with the original 5-HT hypothesis of SAD, a number of treatment efficacy studies have since demonstrated that agents that enhance brain 5-HT transmission, such as *d*-fenfluramine (O'Rourke et al., 1989), tranylcypromine (Dilsaver and Jaekle, 1990), fluoxetine (Ruhman et al., 1993; Childs et al., 1995; Lam et al., 1995), moclobemide (Partonen and Lönnqvist, 1996), and tryptophan (McGrath et al., 1990; Lam et al.,

1997) alleviate the symptoms of winter depression. Similarly, high carbohydrate meals, which increase brain 5-HT content (Fernstrom and Wurtman, 1971), are 'craved' by depressed patients with SAD (Rosenthal et al., 1989; Krauchi et al., 1990), while rapid tryptophan depletion, which lowers brain 5-HT (Moja et al., 1989), reverses the antidepressant effects of both light therapy (Lam et al., 1996; Neumeister et al., 1997; Neumeister et al., 1998b) and summer (Neumeister et al., 1998a) in remitted patients with SAD.

Neuroendocrine challenge studies have also provided support for the 5-HT hypothesis of SAD. Probes administered have included the 5-HT precursor 5-hydroxytryptophan (Jacobsen et al., 1987), the 5-HT_{2C} partial agonist meta-chlorophenylpiperazine (*m*-CPP) (Joseph-Vanderpool et al., 1993; Jacobsen et al., 1994; Garcia-Borreguero et al., 1995; Schwartz et al., 1997a; Levitan et al., 1998), the non-specific 5-HT releasing agent *dl*-fenfluramine (Coiro et al., 1993; Yatham and Michalon, 1995), the 5-HT_{1D} antagonist sumatriptan (Yatham et al., 1997), and ovine-corticotropin releasing hormone (Joseph-Vanderpool et al., 1991). In two of these studies, diminished growth hormone responsivity has been found in patients with SAD (Schwartz et al., 1997a; Yatham et al., 1997). Mixed results have been found with regard to prolactin (Coiro et al., 1993; Garcia-Borreguero et al., 1995; Schwartz et al., 1997a; Levitan et al., 1998). The most frequently (Joseph-Vanderpool et al., 1991; Coiro et al., 1993; Schwartz et al., 1997a), albeit inconsistently (Jacobsen et al., 1987; Garcia-Borreguero et al., 1995; Yatham and Michalon, 1995; Levitan et al., 1998) replicated neuroendocrine abnormality has been a blunted responsivity of the hypothalamic–pituitary–adrenal (HPA) axis to various probes in patients with SAD.

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