



Neuroendocrine effects of citalopram infusion in anorexia nervosa

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Summary Because of the role of serotonin (5HT) in regulating food intake and mood, several studies have focused their attention on the assessment of serotonergic activity in eating disorders, and in particular in anorexia nervosa, but the results have been inconsistent. Citalopram, a highly selective 5HT reuptake inhibitor, has been recently reported as a neuroendocrine probe to assess the serotonergic function in physiological and pathological conditions. We evaluated the adrenocorticotrophic hormone (ACTH), cortisol, prolactin (PRL) and growth hormone (GH) secretion during placebo or citalopram IV infusion (20 mg over 120 min), in six women with anorexia nervosa restricter type, and in six healthy women, in order to test the hypothesis that this neurotransmitter system is abnormal in this group of patients. ACTH and PRL secretion was higher during citalopram infusion compared to placebo ($p < 0.05$) in both groups, while cortisol secretion was higher during citalopram infusion only in healthy controls ($p < 0.05$), but not in anorexic patients. GH levels were unaffected by citalopram in both groups. These results demonstrate that serotonergic activation by citalopram affects corticotroph and lactotroph but not somatotroph secretion in anorexic as well as in normal subjects. Our preliminary findings do not support the existence of remarkable alterations in the serotonergic

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control of anterior pituitary function in anorexia nervosa, while there seems to be an impairment of the adrenal function in this group of patients.

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1. Introduction

Serotonergic agonists have been shown to increase prolactin (PRL), adrenocorticotropin (ACTH) and cortisol levels (Power and Cowen, 1992; Raap and Van de Kar, 1999; Lowe et al., 2006). Based on this evidence, neuroendocrine challenge tests with serotonergic agonists have been often used to investigate the activity of the serotonergic system in both physiological and pathological conditions (Power and Cowen, 1992; Raap and Van de Kar, 1999). Less clear is the role of serotonin (5HT) on the growth hormone (GH) secretion in physiological conditions, since serotonergic activation has been reported to increase GH secretion by some but not by all authors; the inconsistencies among these studies about GH response to serotonergic challenges may be function of different serotonergic probes or experimental conditions (Power and Cowen, 1992; Raap and Van de Kar, 1999).

Given the role of 5HT in regulating mood (Harmer et al., 2006) and food intake (Halford et al., 2005), there has been a strong interest in this neurotransmitter's role in eating disorders, and specifically in anorexia nervosa. Kaye et al. hypothesised that people with anorexia nervosa have a trait-related increase in 5HT neuronal transmission, occurring in the pre-morbid state and persisting after recovery (Kaye et al., 2003). However, studies conducted by the same and other authors on the levels of the 5HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in the cerebrospinal fluid, do not support this hypothesis, as they found reduced levels in underweight anorexics and restored levels after weight restoration (Kaye et al., 1988, 1991; Mantzoros et al., 1997). Many studies, including neuroimaging studies on serotonergic receptors, have reported serotonergic alterations in the acute phase of anorexia nervosa, but it is unclear whether these serotonergic alterations in acute phase of the illness are related to starvation rather than to the eating disorder per se (Schmidt, 2003; Frank et al., 2002, 2004; Kaye et al., 2005a, b). Moreover, there are conflicting results from the genetic studies on serotonin receptor polymorphisms (Frank et al., 2002; Gorwood et al., 2003), and different eating disorder subtypes may have different patterns of serotonergic dysregulation, as suggested by the increased brain 5HT_{1A} receptor binding found in

women recovered by binge-purging-type anorexia but not in women recovered by restrictor-type anorexia (Bailer et al., 2005). Therefore, new studies using novel methodologies to assess serotonergic function in anorexia are needed.

Neuroendocrine studies, performed using serotonergic challenge tests in anorexia nervosa, have revealed abnormalities of cortisol and PRL responses, suggestive of a serotonergic impairment in this condition (Brewerton and Jimerson, 1996; Monteleone et al., 1998, 2000; Brambilla et al., 2001; Goodwin et al., 1989; Frank et al., 2001; Hadigan et al., 1995; Ward et al., 1998; Brewerton, 1995). Some discrepancies among studies are likely to reflect different experimental conditions: for example, different phases of the illness and different serotonergic probes used. In fact, anorexic patients in the acute phase of illness show a blunted PRL and cortisol response to *d*-fenfluramine or to meta-chlorophenylpiperazine (mCPP) (Brambilla et al., 2001; Monteleone et al., 1998, 2000; Hadigan et al., 1995), while the PRL response to *l*-tryptophan seems to be preserved in patients with the restrictor subtype (Goodwin et al., 1989). No data are available yet on the ACTH response to serotonergic probes in underweight anorexic patients, while a blunted GH response to *l*-tryptophan has been reported (Goodwin et al., 1989).

Indeed, the discrepancies among various neuroendocrine studies using serotonergic challenges are not surprising, if we consider that these serotonergic compounds not only are different in their mechanisms of action but also have mixed pharmacological effects. The 5HT precursors, like 5-hydroxytryptophan or *l*-tryptophan, increase the synthesis of 5HT in the nerve terminals. In contrast, 5HT releasing drugs, like fenfluramine, *d*-fenfluramine and mCPP, are taken into the pre-synaptic nerve terminal through the 5HT transporter and induce the release of 5HT, while also having a direct agonist action at post-synaptic 5HT receptors (Raap and Van de Kar, 1999; Rothman and Baumann, 2002). Indeed, the PRL response to *l*-tryptophan seems to be mediated via the post-synaptic 5HT_{1A} receptors (Cowen et al., 1996; Smith et al., 1991), while the PRL responses to *d*-fenfluramine and to mCPP appear to be mediated mainly via activation of post-synaptic 5HT_{2A/2C} receptors (Attenburrow et al., 2001; Cowen et al., 1996).

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