

5-HT_{1A} responsivity in patients with panic disorder before and after treatment with aerobic exercise, clomipramine or placebo

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Abstract

Blunted neuroendocrine and physiological responses to the selective 5-HT_{1A} receptor agonist, ipsapirone, have been observed in patients with panic disorder and/or agoraphobia (PDA). In order to examine whether this hyporesponsiveness to ipsapirone is modified by pharmacological or non-pharmacological therapeutic interventions, challenges with an oral dose of ipsapirone (0.3 mg/kg) and placebo were performed in patients with PDA before and after 10 weeks of treatment with clomipramine, aerobic exercise and placebo. Before treatment, administration of ipsapirone was followed by significant increases of cortisol, anxiety and other psychopathological symptoms in comparison to the placebo challenge. In addition, a significant decrease of body temperature was observed. After the 10-week treatment period, the psychological responses to ipsapirone were significantly reduced in the clomipramine and the exercise group. In contrast, there was a non-significant trend towards higher cortisol responses after clomipramine and exercise treatment. The hypothalamic response to ipsapirone was significantly reduced by clomipramine treatment. In conclusion, our results demonstrate that effective treatment of panic disorder has divergent effects on the psychological, neuroendocrine and temperature responses to ipsapirone.

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1. Introduction

Indices of abnormal serotonergic function have been reported in patients with panic disorder and/or agoraphobia (PDA). In particular, there is evidence for an increased sensitivity of the 5-HT_{2C} subsystem (Benjamin et al., 1999; Broocks et al., 2000; Charney et al., 1987a,b; Kahn et al., 1988a,b; Kahn and Wetzler, 1991; Klein et al., 1991; Wetzler et al., 1996). In contrast, stimulation of 5-HT_{1A} receptors by ipsapirone was followed by an attenuated hypothalamic and ACTH/cortisol response in patients with PDA (Broocks et al., 2000; Lesch et al.,

1992). Further evidence for the involvement of serotonergic pathways in the pathophysiology of panic disorder comes from the observation that serotonin reuptake inhibitors (SSRIs) are of particular benefit in the treatment of PDA (Asnis et al., 2001; Bell and Nutt, 1998; Black et al., 1993; Boyer, 1995; Kasper and Resinger, 2001; Modigh et al., 1992; Otto et al., 2001; Perna et al., 2001; Roy et al., 2001; Sheehan, 1999; Zohar and Westenberg, 2000).

In healthy controls, ipsapirone produces dose-dependent increases in plasma cortisol and ACTH as well as dose-dependent reductions in body temperature (Kahn et al., 1994; Lesch et al., 1989). Ipsapirone acts on specific serotonergic mechanisms in the brain through its high-affinity binding to the 5-HT_{1A} receptor subtype. The binding sites are predominantly located on serotonergic neurons in the raphe nuclei (presynaptic autoreceptors) and

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in limbic structures (postsynaptic receptors). Agonistic properties at presynaptic somatodendritic sites have been observed, resulting in decreased serotonergic neurotransmission (Peroutka, 1985). Concerning the high selectivity of ipsapirone it has to be considered that its metabolite 1-(2-pyrimidinyl)-piperazine (1-PP) has been found to exert antagonistic effects at pre- and postsynaptic alpha 2-adrenoceptors (Blier et al., 1991; Miller et al., 1992).

Ipsapirone induces cortisol secretion via release of ACTH rather than by direct action on the adrenal gland (Przegalinski et al., 1989). The assumption that ipsapirone's hypothermic effect and the stimulation of ACTH and cortisol primarily reflect 5-HT_{1A} receptor function is also supported by the observation that these responses can be antagonized by 5-HT_{1A} receptor antagonists (Goodwin et al., 1987; Hamon et al., 1987) and by recent findings confirming the utility of hypothermia as robust in-vivo probe of 5-HT_{1A} receptor function (Cryan et al., 1999; Oerther and Ahlenius, 2001). However, there is evidence, that the cortisol and the temperature response to ipsapirone might be mediated by different postsynaptic mechanisms (Lerer et al., 1999).

So far, it has not been examined whether psychological and neuroendocrine responses to ipsapirone are modified by pharmacological and non-pharmacological therapies in patients with panic disorder. We hypothesized, that the blunted neuroendocrine and hypothermic responses to ipsapirone in panic disorder are reversed with successful treatment. Therefore, we performed neuroendocrine challenges using ipsapirone and placebo in patients with PDA before and after 10 weeks of treatment with clomipramine, aerobic exercise or placebo.

2. Experimental procedures

2.1. Subjects

Forty-six patients with a diagnosis of moderate to severe panic disorder with or without agoraphobia (PDA) according to DSM-IV and ICD-10 criteria (age range 18 to 50 years) were recruited by physician referral and from the Outpatient Anxiety Disorders Unit of the Department of Psychiatry at the University of Göttingen for participation in a treatment study, which has been reported elsewhere (Broocks et al., 1998). Overall, nine out of the 46 patients did not finish the 10-week treatment protocol and were therefore not eligible to repeat the challenges. From the remaining 37 patients, four patients had not performed the initial challenges, so they could not be asked to repeat the procedure. Finally, 28 patients (from the remaining group of 33 patients) were willing to undergo a second set of challenges after completion of the treatment phase; five patients withdraw saying that they did not feel well during the initial challenges or that they had no time to repeat this

procedure. These five patients did not differ from the completers in terms of age, sex distribution, duration of illness, severity of the disorder and degree of improvement; two out of the five refusers had responded well to the treatment but were not willing to repeat the challenges. In summary, 12 out of 15 patients in the clomipramine group (80%), nine out of 11 in the exercise group (81%) and seven out of 11 patients in the placebo group (64%) completed the challenge study.

Statistical analysis revealed that this subgroup of 28 challenge completers did not differ from the original sample of the 46 patients who entered the treatment study with respect to age, sex distribution, duration and severity of the disorder.

Diagnoses were made by an experienced psychiatrist using the Structured Clinical Interview for DSM-III-R. The following scales were used to assess the severity of the condition: Hamilton Anxiety Scales (HAMA) (Hamilton, 1969), Banelow Panic and Agoraphobia Scale (observer-rated version: PAS-O, patient-rated version: PAS-P (Banelow, 1995, 1999), Clinical Global Impression (rater version: CGI, patient version: PGI (NIMH, 1976). Exclusion criteria were pregnancy, lactation, significant medical illness, bipolar affective disorder, psychotic symptoms, drug dependency (alcohol, benzodiazepine or other), anorexia or bulimia nervosa, and body weight below 80% of ideal body weight. All patients were in good physical health and had a normal physical examination, electrocardiogram, and routine laboratory tests (renal, hepatic, pancreatic, hematological and thyroid functions) prior to inclusion in the study. Patients taking psychotropic medication were required to discontinue this medication at least 3 weeks before baseline. During this time, only single doses of promethazine (25–50 mg) were allowed in the case of severe panic attacks. No medication was allowed 48 h prior to the challenge. Urine analysis for benzodiazepine intake was performed in all patients.

Challenges were conducted in a randomized double-blind fashion on separate days. There was an interval of at least 48 h between two challenges.

The trial was approved by the Ethics Committee of the Medical Faculty of the University of Göttingen.

2.2. Challenge procedures

On the day of each challenge session, subjects arrived at the sleep laboratory of the Department of Psychiatry at approximately 12:30 for a small standardized meal. During the challenge sessions, subjects abstained from eating or sleeping and remained supine with the head elevated. At 13:00, an intravenous catheter was placed in an antecubital vein for repeated blood sampling. At 14:30, 2–4 capsules of either ipsapirone (0.3 mg/kg) or placebo were administered orally.

Behavioral effects were assessed using the Acute Panic

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