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Influence of single-dose quetiapine on fear network activity – A pharmaco-imaging study

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ABSTRACT

Objective: Anxiety disorders are among the most frequent psychiatric disorders. Current treatment guidelines recommend antidepressants, the calcium modulator gabapentin, and benzodiazepines as pharmacological treatments. However, delayed onset of action precludes the use of antidepressants as an acute treatment, while benzodiazepines can be recommended only as an emergency treatment due to their inherent risk of dependence. Therefore, an alternative pharmacological agent with acute efficacy is needed. Preliminary evidence points towards possible anxiolytic properties of the atypical antipsychotic quetiapine. The goals of this study were to test the acute anxiolytic properties of quetiapine in patients suffering from arachnophobia in a challenge paradigm, and to assess the effects of quetiapine on the central nervous fear network.
Methods: In a randomized, double-blind, placebo-controlled proof-of-concept study, n = 58 arachnophobic patients underwent an fMRI scan while looking at phobia-related and neutral stimuli. Subjective anxiety was evaluated retrospectively in questionnaires.
Results: The functional imaging data revealed that patients showed stronger amygdala activation to phobia-related than to neutral stimuli. However, no effect of quetiapine on fear network activity was detected. Further, on questionnaire measures, quetiapine significantly reduced somatic anxiety symptoms, but had no effect on general psychological anxiety.
Conclusion: Viewing phobic pictures resulted in a robust amygdala activation in arachnophobic patients. Quetiapine seems to have no influence on activation in anxiety-related brain areas but appears to reduce acute somatic anxiety symptoms in patients with specific phobia. The central nervous correlates of the anxiolytic effects of quetiapine remain to be clarified in future studies.

1. Introduction

Anxiety disorders are counted among the most frequent psychiatric disorders and are associated with a high economic burden (Kessler et al., 2005; Rice and Miller, 1998; Wittchen et al., 2011). With regard to pharmacological treatment, especially selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs), as well as the anticonvulsant pregabalin, are recommended according to current guidelines (Bandelow et al., 2008). However, up to about a third of patients do not respond sufficiently (Barlow, 2002).

Abbreviations: ACC, anterior cingulate cortex; AE, Adverse event; API, Acute Panic Inventory; ASI, Anxiety Sensitivity Index; BAI, Beck Anxiety Inventory; CCG, calcarine gyrus; FEE, Questionnaire for the Assessment of Disgust Sensitivity; FFG, fusiform gyrus; FSQ, Fear of Spiders Questionnaire; IAPS, International Affective Picture System; IFG, inferior frontal gyrus; IOG, inferior occipital gyrus; ITG, inferior temporal gyrus; LLG, lingual gyrus; MNI, Montreal Neurological Institute; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PHG, parahippocampal gyrus; POMS D, F, V, H, Profile of Mood States Dejection, Fatigue, Vigour, Hostility; SAM, Self-Assessment Manikin; SFG, superior frontal gyrus; SOG, superior occipital gyrus; VAS, Visual Analogue Scale.

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Delayed onset of action is a significant disadvantage of antidepressants (Bandelow et al., 2008), while benzodiazepines, which offer rapid onset of action, carry a marked risk of tolerance and dependency, which limits their use to emergency situations (Lader, 2011). Thus, alternative pharmacological options are still needed.

In accordance with clinical experience, an increasing number of studies report anxiolytic properties of atypical antipsychotics in patients with anxiety disorders (for a review see Gao et al., 2006; Depping et al., 2010). In particular, quetiapine has been associated with anxiolytic effects in patients suffering from social phobia (Schutters et al., 2005: N = 13; Vaishnavi et al., 2007: N = 15) and generalized anxiety disorder (GAD) (Albert et al., 2016; Bandelow et al., 2010; Maneeton et al., 2016; Merideth et al., 2012). Moreover, some evidence points towards an early onset of action (Bandelow et al., 2010; Diemer et al., 2013).

1.1. Rationale for this study

While increasing evidence points towards anxiolytic effects of quetiapine on clinical anxiety symptoms, little is known about its effects on neural correlates of fear network activity. With regard to anxiety, a distorted cortico-limbic control has been suggested by several studies suggesting a dysfunction of prefrontal cortical regions along with a hyperacitivity of the amygdala (Milad and Rauch, 2007; for a review, see Dresler et al., 2013). Thus, this study was designed in order to identify potential effects of the atypical antipsychotic quetiapine on amygdala activity. Moreover, we were interested in whether such potential effects would be correlated with anxiolytic effects.

Pharmacological fMRI, the investigation of pharmacological effects in the brain using fMRI, represents a growing research field (Honey and Bullmore, 2004). Specifically, a number of studies have demonstrated pharmacological effects of anxiolytic drugs on amygdala reactivity to emotional stimuli, as reviewed by Patin and Hurlemann (2011). With regard to "classical" anxiolytics, Paulus et al. (2005) found a significantly decreased response of the bilateral amygdala and insula to emotional faces after a single dose of 1.0 mg lorazepam. This effect was dose-dependent, as no effects were observed after 0.25 mg lorazepam (Paulus et al., 2005).

As for atypical antipsychotics, Takahashi et al. (2005) tested the acute effect of 25 mg of the atypical antipsychotic sultopride in healthy men exposed to neutral and unpleasant IAPS pictures. Sultopride reduced activity in the left amygdala and other areas (Takahashi et al., 2005). The authors related this effect to the D_2-antagonsim of the drug. Conversely, dextroamphetamine, a dopamine agonist, has been shown to increase right amygdala response to angry and fearful faces (Hariri et al., 2002). Taken together, these studies demonstrate the utility of a pharmaco-imaging approach to investigate acute pharmacological effects on the reactivity of the fear network to anxiety-related stimuli.

The presentation of phobia-related picture stimuli has proven a reliable method of inducing acute anxiety and analysing its functional correlates in fMRI in phobic subjects. Arachnophobic patients were found to show higher amygdala activity during the presentation of spider-related stimuli compared to neutral stimuli, and to controls (Dilger et al., 2003; Schienle et al., 2005; Straube et al., 2006).

Thus, in a pharmaco-functional magnetic resonance tomography (phMRI) study, we applied this challenge paradigm in a proof-of-concept design in order to evaluate potential effects of quetiapine on neural functioning in arachnophobic patients.

We expected amygdala reactivity during presentation of anxiety-relevant picture stimuli to be attenuated in the quetiapine group vs. placebo. Further, we hypothesised that subjective anxiety symptoms in response to the fMRI exposure challenge would be significantly lower in the quetiapine group compared to placebo.

2. Methods

2.1. Patient population

N = 60 patients suffering from arachnophobia were recruited via local media advertisements. Details about study inclusion and exclusion criteria are provided by Diemer et al. (2013). Exclusion criteria pertinent to MRI procedures were: a cardiac pacemaker or defibrillator; cochlear or metallic implant or injury by a metallic object that was not removed; weight exceeding the 300 lbs/136 kg weight limit of the scanner bed; use of an Intra-Uterine Device (IUD) with metal components; and claustrophobia. The study was approved by the local ethics committee and carried out in accordance with the Declaration of Helsinki, the rules of Good Clinical Practice and the uniform requirements published by the International Committee of Medical Journal Editors.

2.2. Study design and drug administration

This is a double-blind, randomized, placebo-controlled parallel-group study. We exposed n = 60 patients with arachnophobia to an fMRI exposure challenge 6 h after administration of a single dose of 100 mg quetiapine XR or placebo. Randomization was done by AstraZeneca, who supplied the study medication. AstraZeneca applied a block randomization protocol with 4 patients/block and a 1:1 schedule of quetiapine: placebo. Study medication was sent to the study centre in individually sealed containers and a unique medication number per dose. Medication was dispensed sequentially by number to the patients as they were included in the study. This way, all study staff and patients were blinded to treatment allocation. After the end of the study and after database lock, the randomization list was retrieved from AstraZeneca.

2.3. Assessment instruments

2.3.1. Questionnaires

We employed *Visual Analogue Scales (VAS)* for Anxiety, Anxiety Expectancy, Avoidance, Tension, and Sedation. Further, we administered the *Fear of Spiders Questionnaire (FSQ)* (Szymanski and O'Donohue, 1995), the *Beck Anxiety Inventory (BAI)* (Beck et al., 1988), the *Profile of Mood States (POMS)* (McNair et al., 1992), and the *Acute Panic Inventory (API)* (Dillon et al., 1987) with the three subscales "physical symptoms", "cognitive symptoms", and "fear" (Goetz et al., 1996). The *Anxiety Sensitivity Index (ASI)* (Reiss et al., 1986) and the *Questionnaire for the Assessment of Disgust Sensitivity (Fragebogen zur Ekelempfindlichkeit, FEE)* (Schienle et al., 2002) were included as trait measures.

The questionnaires were administered at baseline and immediately after fMRI exposure. At the latter assessment, subjects were instructed to rate their anxiety symptoms on the questionnaires retrospectively for the most aversive moment during the fMRI exposure. ASI and FEE were presented at baseline only.

2.3.2. Reaction time (RT), measured online

To check for general sedative effects of quetiapine, patients were instructed to respond to each new picture with a button press (right hand, index finger). Reaction times were registered online. Button press was practised on a desktop computer in reaction to neutral pictures before participants entered the scanner.

2.3.3. Manipulation check

After the fMRI scan and the administration of questionnaires, participants were asked to rate each of the 60 spider pictures on 5-point (0 to 4) Self-Assessment Manikin (SAM; Lang et al., 2005) scales for valence and arousal. Picture stimuli were presented as colour printouts in a catalogue that participants perused in their own time.