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Evidences for the involvement of sigma receptors in antidepressant like effect of quetiapine in mice

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ABSTRACT

Although quetiapine is routinely used in the treatment of schizophrenia and bipolar disorders, the precise mechanism of its antidepressant activity is poorly understood. Since quetiapine binds with sigma receptor, the possibility exists that antidepressant action of quetiapine may be mediated through interaction with sigma receptors. In the present study, quetiapine [40–80 μg/mouse, intracerebroventricular (i.c.v.) and 40 mg/kg, intraperitoneal (i.p.)], $sigma_1$ receptor agonist, (+)-pentazocine (120 μg/mouse, i.c.v.) and $sigma_2$ receptor agonist, PB-28 [1-Cyclohexyl-4-[3-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)propyl]piperazine] (20 μg/mouse, i.c.v.) significantly decreased immobility time in forced swim test. In combination studies, the antiimmobility effect of quetiapine (20 μg/mouse, i.c.v.) was significantly potentiated by pretreatment with (+)-pentazocine (30 and 60 μg/mouse, i.c.v.) or PB-28 (5 and 10 μg/mouse, i.c.v.). Conversely, prior administration of $sigma_1$ receptor antagonist, BD-1063 [1-[2-(3,4-Dichlorophenyl)ethyl]-4-methylpiperazine] and $sigma_2$ receptor antagonists, SM-21 [(±)-Tropanyl 2-(4-chlorophenoxy)butanoate] antagonized the antiimmobility effect induced by quetiapine and its synergistic combination with sigma receptor agonists. These results demonstrated the involvement of sigma receptors in the antidepressant like effect of quetiapine and suggest that sigma receptors can be explored as a potential therapeutic target for the treatment of depressive disorders.

1. Introduction

Quetiapine is an atypical antipsychotic routinely used for the treatment of schizophrenia and bipolar disorders. The antipsychotic effect of quetiapine has been linked with its antagonistic activity at 5-HT_2 and dopamine D_2 receptors (Gefvert et al., 1998). Antidepressant profile of quetiapine differentiates it from other typical and atypical antipsychotic drugs (Calabrese et al., 2005; Thase et al., 2006). The mechanism of this antidepressant activity is currently unknown, however suggested to be partially associated with agonistic activity at $5HT_{1A}$ receptors and increased prefrontal cortex dopaminergic neurotransmission in brain (McIntyre et al., 2007). It is now well accepted that dopaminergic neurotransmission plays an important role in the pathogenesis of depression as the agents that modulate dopamine function (precursors, agonists and reuptake inhibitors) in the brain are reported to possess antidepressant property (Kapur and Mann, 1992).

Quetiapine also binds with high affinity to sigma (σ) receptors (Guitart et al., 2004). Sigma receptors exists in two subtypes, $sigma_1$ (σ_1) and $sigma_2$ (σ_2) and proposed as a putative therapeutic target for several psychiatric diseases including depression, anxiety, schizophrenia, drug addiction and neurodegenerative disorders (Cobos et al., 2008; Guitart et al., 2004; Martin-Fardon et al., 2007; Maurice and Romieu, 2004; Monnet and Maurice, 2006). Sigma receptors are abundantly localized in brain areas implicated in the pathophysiology of depression (Aan het Rot et al., 2009; Drevets et al., 2008) including the hippocampus, frontal cortex, hypothalamus, and olfactory bulb (Itzhak et al., 1985, 1991). The activation of σ receptors by selective or non-selective σ receptors agonists including, dio-tolylguanidine (DTG), igmesine, (+)-pentazocine, SA 4503 and UMB23 produce antidepressant like effect in animal models of depression (Matsuno et al., 1996; Ukai et al., 1998; Skuza and Rogoz, 2002; 2003; Wang et al., 2007b) possibly through modulation of glutamatergic, serotonergic, adrenergic and dopaminergic neurotransmission in brain (Kobayashi et al., 1997; Matsuno et al., 1996; Wang et al., 2007a). Conversely, pre-treatment with the σ receptor antagonists BD 1047 [*N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine] or NE 100 [4-Methoxy-3-(2-phenylethoxy)-*N*,*N*-dipropylbenzeneethanamine] abolished the antidepressant-like effect induced by σ receptors agonists (Matsuno et al., 1996; Wang et al., 2007b). Further, σ_1 receptors knockout mice showed high immobility response in the forced swim test (Sabino et al., 2009). It is important to note that, several clinically used antidepressants and endogenous neurosteroids with antidepressant activity such as pregnenolone possessed affinity for σ receptors (Dhir and Kulkarni, 2008;

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Fishback et al., 2010; Maurice and Romieu, 2004; Su et al., 1990). Interestingly, quetiapine also exhibits strong affinity toward σ receptor (Guitart et al., 2004). However, the role of σ receptors in antidepressant like effect of quetiapine remained unexplored.

We hypothesized that antidepressant like effect of quetiapine might involve modulation of σ receptors. The present study explored the involvement of σ_1 and σ_2 receptor subtypes in antidepressant like effect of quetiapine using mouse forced swim test.

2. Materials and methods

2.1. Subjects

Male Swiss mice (25–30 g) were housed under controlled environmental condition at 24 ± 1 °C under 12:12 h light/dark cycle (lights on 07:00–19:00 h) during the experiment. Food and water was available ad-libitum. All experimental procedures were approved by Institutional Animal Ethical Committee and executed according to guidelines given by Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Ministry of Environment and Forests; Government of India; New Delhi.

2.2. Drugs and administration

Quetiapine fumarate, (+)-pentazocine and PB 28 [1-Cyclohexyl-4-[3-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)propyl]-piperazine], were obtained from Sigma chemicals, St. Louise, USA. SM 21 maleate [(±)-Tropanyl 2-(4-chlorophenoxy)butanoate maleate] and BD 1063 [1-[2-(3,4-Dichlorophenyl)ethyl]-4-methylpiperazine] were obtained from Tocris Bioscience, Missouri, USA. All drugs were dissolved in artificial cerebrospinal fluid (aCSF) [composition: 125 mM NaCl, 10 mM glucose, 1.25 mM NaH_2PO_4, 2.5 mM $CaCl_2$, 1.5 mM $MgSO_4$, 26 mM $NaHCO_3$, adjust pH to 7.4 with 0.1 M NaOH] just before the experiments and infused by intra cerebroventricular (i.c.v.) route in volume of 2 μl/side bilaterally. For intraperitoneal (i.p.) administration, drugs were dissolved in sterile saline.

2.3. Intracerebroventricular (i.c.v.) cannula implantation

The detailed procedure for i.c.v. cannulation was described in our previous report (Kotagale et al., 2010). Briefly, mice were anesthetized with an i.p. injection of pentobarbitone sodium 60 mg/kg. The guide cannulae (C_{315} GH/4/SPC, Plastic one Virginia, USA) was implanted bilaterally into the third ventricle using stereotaxic coordinates, ±0.7 mm posterior, ±0.2 mm bi-lateral to midline, ±2 mm ventral from bregma (Paxinos and Franklin, 1997). A 28-gauge dummy cannula (C_{315} 1H/4/SPC, Plastic one Virginia, USA) was inserted to occlude the guide cannula when not in use. After surgery, the animals were placed individually in cages and allowed to recover for 7 days during which they were handled to condition for future experimental procedure. They were treated with oxytetracyclin (25 mg/kg, intramuscular) and neosporin ointment to avoid any infection. The i.c.v. injections were given by 33-guage internal cannula (internal diameter 0.18 mm and outer diameter 0.20 mm), which was attached to a Hamilton microliter syringe (10 μl) via polyethylene tubing (PE-10) (internal diameter, 0.28 mm; outer diameter, 0.61 mm), that extended 0.5 mm beyond the guide cannula. The internal cannula was held in position for another 1 min before being slowly withdrawn to prevent backflow and promote diffusion of drug (Geiger et al., 2008).

At the end of the experiment, dilute India ink was injected by i.c.v. route and the animals were euthanized by an overdose of pentobarbital sodium (80 mg/kg, i.p.). Immediately, the brain of mouse was dissected out and cannula placement was verified histologically for distribution of ink in the ventricles. The guide cannulae were found to be incorrectly placed in some animals (15%) and these were excluded from the observations. Data from only those animals with uniform distribution of ink in the ventricles were considered for statistical analysis.

2.4. Assessment of antidepressant activity

2.4.1. Forced swim test

Forced swim test (FST) was performed to assess antidepressant activity. The immobility time in FST was measured by the observer blind to the treatment using procedure described by Porsolt et al. (1977) with slight modification (Hirani et al., 2002; Taksande et al., 2009). Briefly, mice were placed individually in plexiglass cylinders (21 cm height—12 cm internal diameter) containing fresh water up to a height of 9 cm at 25+1 °C and forced to swim for 15 min as "pretest session" to maintain consistency in the basal immobility time between different groups. After 24 h, the animals were randomly divided into different groups (6–8 animals/group) and treated with either a drug (test group) or vehicle (control group) 30 min before "test session". Each mouse was again forced to swim in a similar environment for the period of 6 min in a "test session" and immobility time was measured. A mouse was judged to be immobile when it remained floating motionless in the water, making only necessary movements to keep its head above water. Each mouse was used only once in "test session". Reduction in the duration of immobility was considered as antidepressant like effect of the drug.

2.5. Dose specific effect of quetiapine and σ receptor ligands on immobility time in FST

This experiment examined the dose dependent effect of quetiapine, σ receptor agonists or antagonists on immobility time in FST. Different group of mice (n=6) were administered with various doses of quetiapine [(10, 20, 40 mg/kg, i.p.); (20, 40, 80 μg/mouse, i.c.v.)] or saline (10 ml/kg, i.p.) or aCSF (2 μl/mouse, i.c.v.). Thirty min later each mouse was subjected to FST for 6 min and the duration of immobility was measured.

In separate group of experiments, mice (n=6) were treated with either (+)-pentazocine (30, 60, 120 μg/mouse, i.c.v., σ_1 receptor agonist), PB-28 (5, 10, 20 μg/mouse, i.c.v., σ_2 receptor agonist), BD-1063 (5, 10, 20 μg/mouse, i.c.v., σ_1 receptor antagonist), SM-21 (2.5, 5, 10 μg/mouse, i.c.v., σ_2 receptor antagonist) or aCSF (2 μl/mouse, i.c.v.) and 30 min thereafter immobility time was measured in the "test session".

2.6. Influence of σ receptor agonists on quetiapine induced antidepressant like effect

This experiment examined the antidepressant like effect of quetiapine in animals pretreated with σ_1/ σ_2 receptor agonists. For combination studies subeffective doses of drugs were used. Different groups of mice were pretreated with (+)-pentazocine (30 and 60 μg/mouse, i.c.v.) or PB-28 (5 and 10 μg/mouse, i.c.v.) or aCSF (2 μl/mouse, i.c.v.). Thirty min following these treatments, all animals received subeffective dose of quetiapine (20 μg/mouse, i.c.v.) or aCSF (2 μl/mouse, i.c.v.) and the immobility time was measured for 6 min test session in FST.