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Protective effect of the antipsychotic drug zotepine on dizocilpine-induced neuropathological changes in rat retrosplenial cortex

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Abstract

An atypical antipsychotic drug, zotepine, which is pharmacologically and clinically related to clozapine, has unique therapeutic effects on patients with schizophrenia. It has been demonstrated that clozapine blocks neurotoxicity in the rat retrosplenial cortex induced by administration of the noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist dizocilpine ((+)-MK-801). We examined whether or not zotepine has the ability to block neurotoxicity in the rat retrosplenial cortex induced by administration of dizocilpine. Female Sprague–Dawley rats were injected intraperitoneally (i.p.) with vehicle (1 mg/kg), zotepine (5, 10 or 20 mg/kg) or clozapine (20 mg/kg). Fifteen minutes later, animals were injected intraperitoneally (i.p.) with vehicle (1 ml/kg) or dizocilpine (0.5 mg/kg). Neuropathological changes (neuronal vacuolization) were assessed 4 h after administration of dizocilpine. Immunohistochemical analysis of heat shock protein HSP-70, a marker of reversible neuronal injury, was performed 24 h after administration of dizocilpine. The pretreatment with zotepine (5, 10 or 20 mg/kg) significantly decreased the number of vacuolized neurons in the rat retrosplenial cortex 4 h after the administration of dizocilpine (0.5 mg/kg), in a dose-dependent manner. The potency of zotepine (20 mg/kg) for dizocilpine-induced neurotoxicity was similar to that of clozapine (20 mg/kg). Furthermore, similar to the case with clozapine (20 mg/kg, i.p.), zotepine (20 mg/kg, i.p.) significantly attenuated the expression of HSP-70 in the rat retrosplenial cortex induced by dizocilpine (0.5 mg/kg, i.p.). The present study suggests that the neuroprotective effects of zotepine- on dizocilpine-induced neurotoxicity are equipotent to those of clozapine. Based on the NMDA receptor hypofunction hypothesis of schizophrenia, the efficacy of zotepine in this study may partly contribute to the unique therapeutic effects of zotepine in patients with schizophrenia.

Keywords: Zotepine; Clozapine; Schizophrenia; Glutamate; Dizocilpine (MK-801); (Rat)

1. Introduction

Schizophrenia has traditionally been treated with the so-called typical antipsychotic drugs such as chlorpromazine or haloperidol, which have potent dopamine receptor antagonist properties. These drugs are effective at reducing the positive symptoms of schizophrenia, but are less effective at reducing the incidence of negative symptoms and cognitive deficits of the illness and are also associated with a high incidence of extrapyramidal symptoms. Clozapine, the first drug to be introduced into clinical practice as a so-called atypical antipsychotic drug, maintains efficacy at treating the positive and negative symptoms; clozapine also has a low incidence of extrapyramidal symptoms and it is considered as a first-choice drug for treatment-resistant schizophrenic patients (Kane et al., 1988; Fleischhacker, 1999). However, the risk of agranulocytosis limits the widespread use of clozapine. In the search for other novel antipsychotics that share the efficacy of clozapine without inducing hematological side effects, a multitude of drugs have been developed over the decades.

The chemical structure of zotepine is similar to clozapine, but it is not similar to the typical antipsychotic drugs haloperidol or chlorpromazine (Needham et al., 1996). As regards the issue of multiple receptor interactions, in vitro receptor binding assays have indicated that zotepine shares similar binding properties with clozapine (Richelson and Souder, 2000). Clinically, zotepine has a comparable effi-

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cacy to haloperidol, and superior efficacy to chlorpromazine in the treatment of patients with acute exacerbation of schizophrenia; in addition, zotepine has shown to possess superior efficacy to haloperidol in the treatment of patients with predominantly negative symptoms (Petit et al., 1996; Cooper et al., 2000). Furthermore, zotepine is well tolerated and is associated with fewer side effects, particularly as regards extrapyramidal symptoms, than the typical antipsychotic drugs (Petit et al., 1996; Cooper et al., 2000). Interestingly, in a comparative trial versus clozapine, zotepine was shown to possess equivalent efficacy to clozapine in terms of improving both positive and negative symptoms, as well as cognitive deficits of treatment-resistant schizophrenic patients (Meyer Lindenberg et al., 1997). In addition, zotepine also has been shown to have a therapeutic profile in bipolar patients (Harada and Otsuki, 1986; Dieterle et al., 1987).

Neuronal vacuolization of the rat retrosplenial cortex has been reported as one of the characteristic neuropathological changes induced by *N*-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine and ketamine (Olney et al., 1989; Olney and Farber, 1995), which induce a psychotic state when administrated to humans. Therefore, the NMDA receptor hypofunctional state has been considered as a possible condition leading to psychotic disorders such as schizophrenia (Javitt and Zukin, 1991; Goff and Coyle, 2001; Krystal et al., 1999; Tamminga, 1998; Farber et al., 2002; Hashimoto and Iyo, 2002); NMDA receptor antagonist-treated rodents have been considered to be a more suitable animal model for schizophrenia than other animal models (Gainetdinov et al., 2001). Some drugs have been reported to influence the prevention or reduction of the neurotoxicity of NMDA receptor antagonists in studies using the neuronal vacuolization of rodent retrosplenial cortex as an index of the neurotoxicity of NMDA receptor antagonists (Farber et al., 2002). Antipsychotic drugs including clozapine, but not haloperidol, have been shown to block the neuronal vacuolization caused by dizocilpine (Olney and Farber, 1994; Hashimoto et al., 2000; Fujimura et al., 2000). However, no report on zotepine's efficacy for NMDA receptor antagonist-induced neurotoxicity has been published to date.

The heat shock or stress genes are induced by a wide variety of stimuli including heavy metals, heat, oxidative and ischemic stress, prolonged seizures, hypoglycemia, calcium ionophores and certain toxins. It is suggested that heat shock proteins may play important roles in cellular repair and/or protective mechanisms (Brown, 1995). It has been shown that heat shock protein HSP-70, which is known as a sensitive marker of reversible neuronal damage, was induced in the retrosplenial cortex of the rat brain after administration of noncompetitive NMDA receptor antagonists such as dizocilpine, phencyclidine and ketamine (Sharp et al., 1991; Hashimoto et al., 1997, 1996).

The present study was undertaken in order to examine the effects of zotepine on neuropathological changes and induction of HSP-70 protein in the rat retrosplenial cortex produced by the NMDA receptor antagonist dizocilpine.

2. Materials and methods

2.1. Animals

Female Sprague–Dawley rats (10–12 weeks old, 190–250 g) were housed under a 12-h light/12-h dark cycle with free access to food and water. In this study, female rats were used, as they are known to be more sensitive than male rats to the neurotoxic effects of NMDA receptor antagonists (Olney et al., 1989). All experiments were carried out in accordance with the Guide for Animal Experimentation (Chiba University, 1991).

2.2. Drug treatment

Animals were injected intraperitoneally (i.p.) with vehicle (0.8% acetic acid), zotepine (Fujisawa Pharmaceutical, Osaka, Japan; 5, 10 or 20 mg/kg) or clozapine (Novartis Pharmaceutical Corporation, Basel, Switzerland; 20 mg/kg). Fifteen minutes later, the animals were injected intraperitoneally (i.p.) with vehicle (distilled water) or dizocilpine (0.5 mg/kg) as a free base.

2.3. Neuropathology

Four hours after the administration of dizocilpine, the animals were deeply anesthetized with sodium pentobarbital (50 mg/kg, i.p.). Ten minutes later, the animals were transcardially perfused with 100 ml of isotonic saline, followed by 400 ml of ice-cold 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). Subsequently, the brains were removed, processed by graded ethanol dehydration, embedded in paraffin, and sectioned into 4-μm-thick coronal slices and stained with hematoxylin and eosin. The brain level of the bregma, −5.80 mm from the atlas of the rat brain (Paxinos and Watson, 1998), was used. Vacuolized neurons in layers III and IV of the retrosplenial cortex of each side of the brain were counted. The number of vacuolized neurons from two slides per subject was averaged for each animal. Counting was performed blind with respect to the treatment group.

2.4. Immunohistochemistry

Immunohistochemistry was performed using a Vectastain Elite ABC kit (Vector Laboratories, Burlingame, CA) as reported previously (Hashimoto et al., 1996, 1997). Twenty-four hours after the administration of dizocilpine, the animals were deeply anesthetized with sodium pentobarbital (30 mg/kg, i.p.). Ten minutes later, the animals were transcardially perfused with 100 ml of isotonic saline, followed by 400 ml of ice-cold 4% paraformaldehyde in 0.1 M

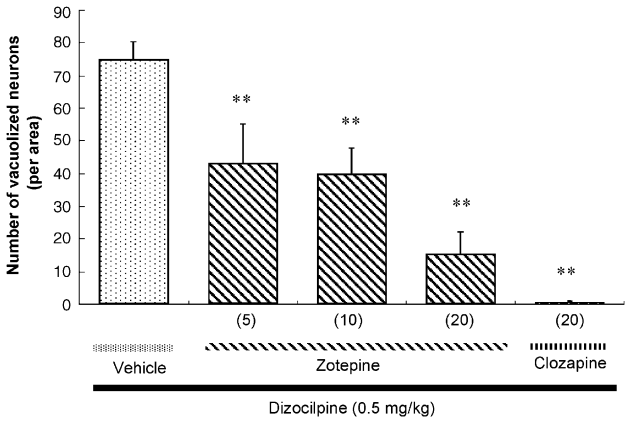

Fig. 1. Effects of pretreatment with zotepine or clozapine on dizocilpine-induced neurotoxicity in the rat retrosplenial cortex. Fifteen minutes after the administration of vehicle (1 ml/kg), zotepine (5, 10 or 20 mg/kg), or clozapine (20 mg/kg), dizocilpine (0.5 mg/kg) was administered to rats. The number of vacuolized neurons in the rat retrosplenial cortex was examined 4 h after the administration of dizocilpine. Each value represents the mean ± S.E.M. for five or six rats. $^{**}P < 0.01$ as compared with the vehicle-treated group (Bonferroni/Dunn method).

phosphate buffer (pH 7.4). The brains were removed, post-fixed for 90 min at 4 °C in the same fixative, and 70-μm-thick coronal sections were cut in ice-cold 0.01 M phosphate buffer saline (PBS; pH 7.4) using a vibrating blade microtome (VT1000S, Leica Microsystems, Wetzlar, Germany). The slices were placed in ice-cold 0.01 M PBS and washed twice in 0.01 M PBS. Free-floating sections were placed in 0.01 M PBS buffer containing 2% horse serum, 0.2% Triton X-100 and 0.1% bovine serum albumin (HS-PBST) for 1 h at room temperature. The samples were incubated for 48 h at 4 °C with a primary antibody to HSP-70 (Stressgen Biotechnologies, Victoria BC, Canada) diluted to 1/1000 in HS-PBST. The sections were washed twice in PBS, incubated for 1 h with a second antibody (biotinylated horse anti-mouse immunoglobulin G; diluted 1/200), and incubated in an avidin-biotinylated horseradish peroxidase solution prepared from a kit for 1 h at room temperature. The sections were washed twice in ice-cold PBS and antibody reaction was developed with 3,3′-diaminobenzidine (0.015%) and 0.001% hydrogen peroxide in 50 mM Tris–HCl (pH 7.4). Following several rinses in PBS, sections were mounted on gelatinized slides, dehydrated through an ethanol gradient, and cleared in xylene and coverslipped with Permount® (Fisher Scientific, Fair Lawn, NJ). Cells expressing HSP-70 protein were counted in the sections containing layers III and IV of the retrosplenial cortex. The number of cells expressing HSP-70 protein from two sections was averaged for each subject.

2.5. Statistical analysis

The data were presented as the mean ± standard error of the mean (S.E.M.), and statistical significance was analyzed by a one-way analysis of variance (ANOVA) followed by Bonferroni/Dunn's post hoc test. The criteria for significance were $^{*}P < 0.05$, $^{**}P < 0.01$.

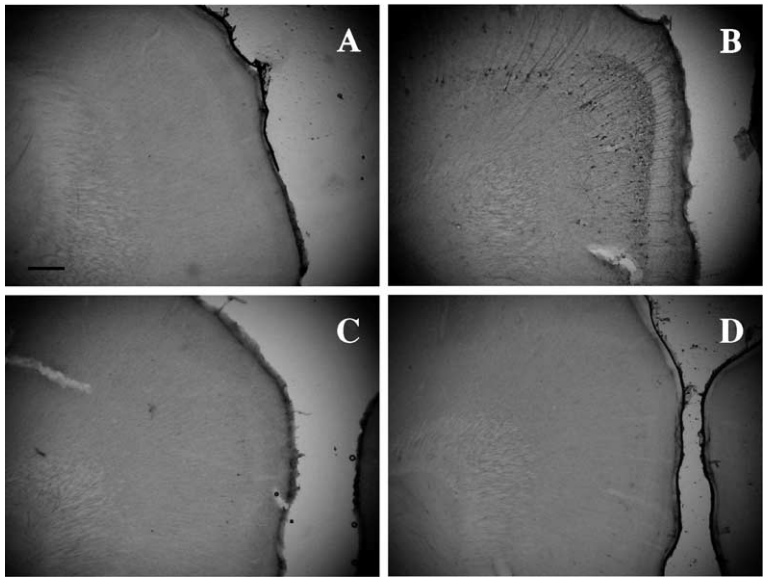

Fig. 2. The expression of HSP-70 immunoreactivity in the rat retrosplenial cortex by the administration of dizocilpine. (A) Vehicle (1 ml/kg) plus vehicle (1 ml/kg). (B) Vehicle (1 ml/kg) plus dizocilpine (0.5 mg/kg). (C) Zotepine (20 mg/kg) plus dizocilpine (0.5 mg/kg). (D) Clozapine (20 mg/kg) plus dizocilpine (0.5 mg/kg). Vehicle or drugs were administered, i.p., 15 min before injection of vehicle or dizocilpine. The HSP-70 immunohistochemical analysis was performed 24 h after the administration of dizocilpine. Scale bar = 200 μm.

3. Results

3.1. Effects of zotepine and clozapine on neuropathological changes in the rat retrosplenial cortex following the administration of dizocilpine

Administration of dizocilpine (0.5 mg/kg, i.p.) induced vacuole reaction in layers III and IV of the retrosplenial cortex, as reported previously (Olney et al., 1989). The pretreatment with zotepine (5, 10 or 20 mg/kg, i.p.) significantly decreased the number of vacuolized neurons in the retrosplenial cortex 4 h after the administration of dizocilpine in a dose-dependent manner (Fig. 1). One-way ANOVA showed significant differences among groups ($F = 11.799$ [4, 24], $P < 0.0001$). Furthermore, pretreatment with clozapine (20 mg/kg, i.p.) significantly decreased the number of vacuolized neurons (Fig. 1). Although clozapine was more potent than zotepine, this difference was not statistically ($P = 0.227$) significant. Treatment with vehicle alone did not induce a vacuole reaction in the rat brain, as had previously been reported (data not shown).

3.2. Effects of zotepine and clozapine on the expression of HSP-70 protein in the rat retrosplenial cortex following the administration of dizocilpine

Administration of dizocilpine (0.5 mg/kg, i.p.) induced the expression of heat shock protein HSP-70 in the retrosplenial cortex, as reported previously (Sharp et al., 1991; Hashimoto et al., 1996, 1997) (Fig. 2B). Similar to clozapine (20 mg/kg, i.p.), pretreatment with zotepine (20 mg/kg, i.p.) significantly decreased the number of HSP-70-expressing neurons in the retrosplenial cortex 24 h after the administration of dizocilpine (Figs. 2B,C and 3). Although zotepine was more potent than clozapine, this difference was not statistically ($P = 0.2059$) significant. Furthermore, treatment with vehicle alone did not induce the expression of HSP-70 immunoreactivity (Fig. 2A).

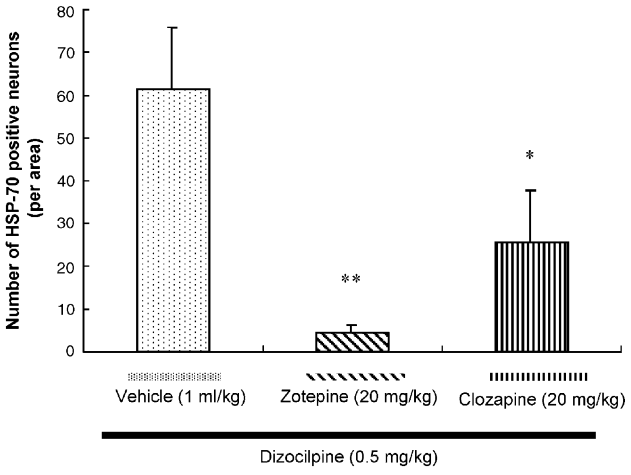

Fig. 3. Effects of zotepine and clozapine on dizocilpine-induced HSP-70 expression in the rat retrosplenial cortex. Fifteen minutes after the administration of vehicle (1 ml/kg), zotepine (20 mg/kg), or clozapine (20 mg/kg), vehicle (1 ml/kg) or dizocilpine (0.5 mg/kg) was administered to the rats. The number of cells expressing HSP-70 protein in the rat retrosplenial cortex was examined 24 h after the administration of dizocilpine. Each value represents the mean ± S.E.M. of five rats. *$P < 0.05$, **$P < 0.01$ as compared with vehicle-treated group (Bonferroni/Dunn method).

4. Discussion

Our results indicate that, similar to clozapine, pretreatment with zotepine protects against neuropathological changes and the expression of heat shock protein HSP-70 in the rat retrosplenial cortex after administration of dizocilpine. The observed protective effects of clozapine against dizocilpine-induced neurotoxicity in the rat retrosplenial cortex are consistent with those of previous reports (Olney and Farber, 1994; Fujimura et al., 2000; Hashimoto et al., 2000). In this study, we found that the efficacy of zotepine on dizocilpine-induced neurotoxicity is equivalent to that of clozapine. As described previously, zotepine has a similar receptor binding profile and a related structural formula to those of clozapine (Needham et al., 1996). Furthermore, it has been reported that zotepine blocked dizocilpine-induced stereotypy and locomotor activity in rats in a dose-dependent manner (Gattaz et al., 1994). Moreover, it has been demonstrated that, similar to clozapine, zotepine causes an elevation in cortical dopamine in freely moving rats at doses relevant to those derived from animal models that predict antipsychotic activity (Rowley et al., 2000). Taken together with our findings, zotepine may partly possess a clozapine-like efficacy in patients with schizophrenia.

It has been hypothesized that NMDA receptor antagonist-induced neurotoxicity is based upon a disinhibition principle; that is, the blocking of NMDA receptors on γ-aminobutyric acid (GABA) neurons leads to inactivation of inhibitory neurons and to the release of major excitatory pathways from inhibition (Olney and Farber, 1995; Olney et al., 1999; Farber et al., 2002). It also has been reported that muscarinic receptor antagonists protect against the neurotoxicity of NMDA receptor antagonists in the retrosplenial cortex, suggesting the role of muscarinic receptors in mediating NMDA receptor antagonist-induced neurotoxicity (Olney et al., 1991, 1999; Olney and Farber, 1995). Unlike clozapine, zotepine does not bind to muscarinic receptors with high affinity (Richelson and Souder, 2000). Therefore, it is unlikely that muscarinic receptors play a role in the protective effects of zotepine on dizocilpine-induced neurotoxicity. It has been suggested that several different receptors may be critical for conferring protection against the neurotoxicity of NMDA receptor antagonists, as clozapine and zotepine interact with a wide range of receptors (Olney and Farber, 1995; Olney et al., 1999). It is currently unclear whether any of the above pharmacological characteristics, or some

combination thereof, account for the unique properties of these drugs.

Preclinical data from trials with zotepine suggest a pharmacological similarity to clozapine, as well as an equivalent efficacy. Several novel atypical antipsychotics have come onto the market in the last decade, though clozapine still remains the first-choice treatment for people with treatment-resistant schizophrenia, in spite of its risk of serious side effects (Fleischhacker, 1999). In a randomized, double-blind study versus clozapine, the comparable efficacy of zotepine has been reported (Meyer Lindenberg et al., 1997). In the study, 50 patients with treatment-resistant schizophrenia were assigned to 6 weeks of treatment with one of the two drugs. The Brief Psychiatric Rating Scale (BPRS) scores and the Scale for the Assessment of Negative Symptoms (SANS) scores were analyzed, and the zotepine and clozapine groups showed no statistical difference as regards the time course of improvements in the BPRS and SANS scores. Though no comparison with a placebo control group was performed, this result indicates that zotepine and clozapine could be equally effective in the treatment of schizophrenia. Furthermore, in a maze test evaluating neurocognitive effects, improvement by medication was evident in both groups, and was even more pronounced in the zotepine-treated group (Meyer Lindenberg et al., 1997). Moreover, another clinical feature that clozapine and zotepine have in common is their antimanic effect. Zotepine has long been known for its efficacy in treating manic patients (Harada and Otsuki, 1986; Puech and Martin, 1987; Dieterle et al., 1987); the results of a double-blind trial versus lithium carbonate in patients with bipolar disorder demonstrated that zotepine was superior to lithium in treating mood disorder. The antimanic effect of clozapine has also been reported previously (Calabrese et al., 1996; Weizman and Weizman, 2001). Taken together, these results suggest that zotepine, which has the same effectiveness as clozapine, would be a potential antipsychotic drug of choice for patients with treatment-resistant schizophrenia; moreover, zotepine has the advantage that it does not possess the potentially lethal hematological side effect profile of clozapine.

In conclusion, the present study indicated that the administration of zotepine is able to significantly reduce neuronal vacuolization in the rat retrosplenial cortex following the administration of the NMDA receptor antagonist dizocilpine; in this study, the effects of zotepine were equivalent to those of clozapine. Furthermore, the protective effects of zotepine on the dizocilpine-induced neurotoxicity may, in part, contribute to the unique antipsychotic effects of zotepine in schizophrenic patients.

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