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Olanzapine attenuates brain damage after focal cerebral ischemia in vivo

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Abstract

Atypical antipsychotic drugs are widely used in the treatment of schizophrenia. These agents are discovered to have some additional beneficial effects beyond their effectiveness as antipsychotic drugs. Among these initially unexpected effects are their potential effects as mood stabilizers in bipolar disorder and their efficacy in improving long-term outcome in schizophrenia. These effects recently raised the question whether these drugs may also have some neuroprotective effect in the brain. To examine this matter, in this study we evaluated the neuroprotective effect of olanzapine after permanent focal cerebral ischemia. Anaesthetized male C57BL/6j mice were submitted to permanent thread occlusion of the middle cerebral artery (MCA). Olanzapine (0.1 and 1 mg/kg) or vehicle was applied intraperitoneally just after permanent ischemia. Twenty-four hours after permanent ischemia, brain injury was evaluated by triphenyltetrazolium chloride staining (TTC). Olanzapine (0.1 and 1 mg/kg) showed significant neuroprotection after permanent focal cerebral ischemia.

Keywords: Olanzapine; Cerebral ischemia; Neuroprotection; Stroke

1. Introduction

Stroke is the third leading cause of death and adult morbidity in developed countries [38,35]. Many molecular mechanisms including the role of massive inflammation have been proposed to explain the pathogenesis of this clinically devastating disease [3,9,21]. Interest in role of neurotransmitters in the pathogenesis of ischemic stroke resulted in studies establishing that release of not only glutamate but also other neurotransmitters (i.e. dopamine and serotonin) and their excitotoxic actions are important for the development of ischemic neuronal damage [15,29,14]. In this respect, the extracelluler release of dopamine and serotonin is shown to be correlated with the extent of the ischemic damage [34,16].

Despite serious progresses in basic neuroscience research which focused also on the endogenous neuroprotective capacity of the brain [30], the translation of these research findings into therapeutic advances for neurological diseases is frustratingly slow. Thus, clinically applicable and experimentally neuroprotective drugs should be studied more than before, i.e. erythropoietin in clinical stroke [10]. Olanzapine is one of the member of the atypical neuroleptic drugs and a candidate as a clinically applicable neuroprotective drug. In addition to its well-known antidopaminergic and antiserotonergic effects, olanzapine is also shown to increase the number of newborn cells in the dentate gyrus and in the prelimbic cortex of the hippocampus [25,45,44]. However, it has also been reported that olanzapine increases the potent GABA(A) receptor modulator allopregnanolone, which is recently proven to be neuroprotective in vitro in cerebral ischemia [28,12].

It is well known that the atypical neuroleptic drugs are widely used in the treatment of schizophrenia and bipolar disorder. These agents, in addition to their superior efficacy profile relative

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to conventional neuroleptic agents for acute treatment of psychotic symptoms are also considered to be more effective for improving long-term outcome in schizophrenia [43,49,50,11,8].

Schizophrenia is also now considered to be a neurodevelopmental and neurodegenerative disease according to the clinical and neuroimaging studies [8,19,13,27]. These results indicate that atypical neuroleptics may have a mechanism of action other than the previously proposed mechanisms, which might explain their role in improved cognition in animals and in schizophrenic patients.

Altogether these findings suggest that atypical antipsychotics with their potential to stimulate neuronal replacement and repair may also be promising in other neurodegenerative diseases.

On the basis of insufficient safety and limited theraupetic time window of thrombolytic therapy in humans, we thought that the permanent focal cerebral ischemia model would have more clinical relevance than the transient cerebral ischemia in this study. However, in addition to the well known antidopaminergic and antiserotonergic effects of olanzapine, the evidences about its neuroprotective effects are rapidly replicating. These factors prompt us to choose olanzapine as a pharmacological agent whereas it was expected that its effects on neurotransmitter (i.e. dopamin and serotonin) and neurosteroid levels (i.e. allopreganolone) would be enough to prevent or delay ischemia in a relevant model for the nonthrombolyzed stroke in humans.

In our study we have examined the effect of olanzapine in the mouse model of focal permanent cerebral ischemia and administered olanzapine just after production of permanent ischemia. Reproducibity of cerebral ischemia was controlled by Laser Doppler Flowometry and the neuroprotection was evaluated by infarct volume measurements.

2. Materials and methods

2.1. Experimental groups

All experimental procedures were carried out with governmental approval according to local guidelines for the care and use of laboratory animals. Adult male C57BL/6j mice weighing 21–25 g was assigned to the following experiments and groups: I. Intraperitoneal administration of (a) 0.1 mg/kg olanzapine ($n = 6$ animals), (b) 1 mg/kg olanzapine ($n = 8$ animals), (c) 0.2 ml vehicle (0.09% NaCl) ($n = 8$ animals), starting at the onset of 24 h of permanent focal cerebral ischemia. Olanzapine (Lilly Chemical Pharmaceuticals) dissolved in 0.1N HCl and then buffered with NaOH (final pH 7.1). By referring to the recommended clinical dose range of 10–20 mg/day of olanzapine in humans and 70–100 times higher metabolic rate in mice we determined averaged doses of olanzapine as 0.1 and 1 mg/kg [37].

2.2. Induction of ischemia

Animals were anesthetized with 1% halothane (30% O_2, remainder N_2O). Rectal temperature was maintained between 36.5 and 37.0 °C using a feedback-controlled heating system. During the experiments, cerebral blood flow was measured by laser Doppler flowmetry (LDF) using a flexible 0.5 mm fiber optic probe (Perimed, Stockholm, Sweden), which was attached to the intact skull overlying the MCA territory (2 mm posterior/6 mm lateral from bregma). LDF changes were monitored up to 30 min after the onset of ischemia.

Focal cerebral ischemia was induced using an intraluminal filament technique [51]. A midline neck incision was made, and the left common and external carotid arteries were isolated and ligated. A microvascular clip (FE691, Aesculap, Tuttlingen, Germany) was temporarily placed on the internal carotid artery. A 8-0 nylon monofilament (Ethilon; Ethicon, Norderstedt, Germany) coated with silicon resin (Xantopren, Bayer Dental, Osaka, Japan; diameter of the coated thread: 190–200 μm) was introduced through a small incision into the common carotid artery and advanced 9 mm distal to the carotid bifurcation for permanent occlusion of the MCA. Anesthesia was discontinued and animals were placed into their home cages.

2.3. Triphenyltetrazolium chloride (TTC) staining

Animals were reanesthetized with overdose halothane and decapitated. Brains were incubated for 5 min in ice-cold isotonic saline and coronally cut into five 2 mm slices using a mouse brain matrix (BRM-2000C; Activational System Inc., MI, USA). These slices were immediately stained with 2% 2,3,5-triphenyltetrazolium chloride (TTC) for 20 min. The border between infarcted and non-infarcted tissue was outlined using an image analysis system, and the area of infarction was measured by subtracting the area of the non-lesioned ipsilateral hemisphere from that of the contralateral side. The infarct volume was calculated by integration of the lesion areas [51,23,24].

2.4. Statistics

All values are given as mean ± S.D. Differences between groups were compared by using oneway ANOVA analysis followed by LSD tests after permanent cerebral ischemia. P values <0.05 were considered to indicate statistical significance.

3. Results

3.1. Laser Doppler flow (LDF)

Mean LDF reproducibly declined to 25% of pre-ischemic control levels immediately after thread insertion in all animal groups. No differences were seen between various animal groups (Fig. 1).

3.2. Triphenyltetrazolium chloride (TTC) staining: infarct size

Reproducible brain infarcts were obtained in the 0.1 and 1 mg/kg of olanzapine or 0.2 ml of vehicle treated groups (Fig. 2). Intraperitoneal administration of 0.1 and 1 mg/kg

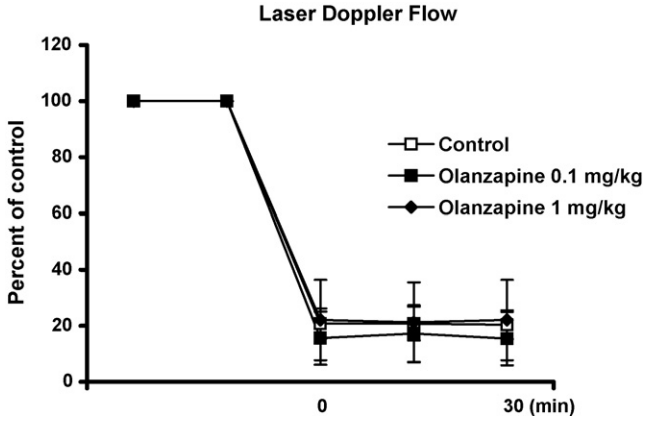

Fig. 1. Laser Doppler flow measurements (LDF) above middle cerebral artery territory during permanent intraluminal thread occlusion in animals treated with vehicle solution or olanzapine. No differences in LDF values were detected between animal groups. Values are mean ± S.D.

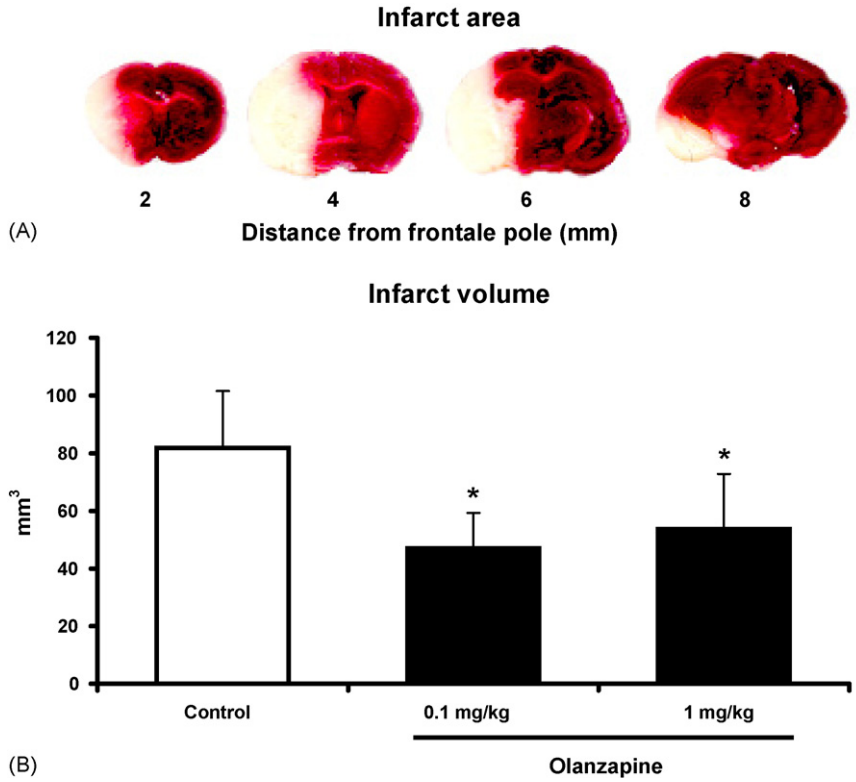

Fig. 2. (A) 2,3,5-Triphenyltetrazolium chloride sections, outlining the infarcted area in a representative mouse subjected to cerebral ischemia. (B) Infarct volumes of mice subjected to permanent cerebral ischemia. Animals treated with olanzapine (0.1 or 1 mg/kg). Note that 0.1 and 1 mg/kg olanzapine lead to a decrease in infarct size. *Significantly different from vehicle-treated control animals ($p \leq 0.05$). Data are given as mean ± S.D.

olanzapine significantly reduced the infarct volume as compared with control animals (Fig. 2).

4. Discussion

In the ischemic brain it is well known that a massive release of dopamine can amplify the neuronal damage caused by excitotoxicity and energy deprivation [4,39,22]. Besides dopamin, serotonin is also shown to modulate the postsynaptic effects of glutamate and leads to reduction of blood flow during cerebral ischemia [33,31]. Therefore, ischemia-induced abnormal release of such neurotransmitters in vulnerable brain areas may represent a critical factor that transforms transient ischemic attack into an ischemic episode resulting in irreversible consequences in brain tissue and its synaptic circuits.

In this respect, we have recently shown that risperidone, an atypical antipsychotic agent with significant 5HT2 and D2 antagonism, decreased the ischemic neuronal injury by mice [52]. Given also the neuroprotective effects of the classical mood stabilizers "lithium and valproate" [42,18,7], clinical evidence suggesting some mood stabilizing effects of the olanzapine would also provide further rationale to investigate neuroprotective effects of this agent. Several investigators have documented that atypical antipsychotics such as quetiapine, olanzapine and clozapine modulate brain derived nerve growth factor (BDNF) expression and B cell lymphoma protein (bcl-2) levels in mice and rat brain after chronic exposure [1,2,46]. Indeed, it has been shown that olanzapine induces an upregulation of superoxide dismutase 1 mRNA (SOD1mRNA) [26] which is an important enzyme responsible for detoxification of free O_2 radicals during cerebral ischemia. In our study we observed that acute administration of 0.1 and 1 mg/kg of olanzapine significantly decreased the infarct size in mice.

To the extent that these data in mice translate to people, it is unlikely that olanzapine worsens neuronal damage caused by small strokes, which elderly patients probably sustain frequently. This finding is interesting in light of recent clinical evidence of an increased rate of cerebrovascular events in olanzapine-treated dementia patients that made it possible to review the evidence for non-pharmacological interventions [48,17,41].

The rate of cerebrovascular accidents was found in the placebo group as 0.4% whereas it was found in the olanzapine-treated group as 1.3% [17]. Because olanzapine provided significant neuroprotection in mice, it might trigger other mechanism(s), including vascular pathology, known to be associated with higher stroke risk in demented patients [36].

Additionally, it is widely known that occurrence of post-stroke mood disorders, especially depression, is one of the most frequent complications of stroke [32]. It affects approximately 20–40% of all patients and the definitive treatment of this clinical picture includes various antidepressant agents [47]. Moreover, besides its well tolerability and mood stabilizing effect, its actually proven neuroprotective property by our study could also

provide strong preclinical evidence to its role as a posssible candidate for post-stroke mood disorders.

In our study we have not observed an additional decreasement of infarct size in the olanzapine 1 mg/kg dose group. It is difficult to estimate what caused that difference without getting the results from further experiments on the antiapoptotic effects of various atypical antipsychotic agents with different receptor affinities. However, there is data indicating enhancing effect of cholinergic activity in neuroprotection as well as reversal of such effect under cholinergic blockage [6,20,5,40]. This together with the knowledge that olanzapine at higher doses exerts anti-cholinergic activity may explain the failure of 1 mg/kg of olanzapine to show an additional neuroprotection. But it should also not to be forgotten that the failure of neuroprotection (by the olanzapine 1 mg/kg dose group) could be related to the limited size of penumbra which could have restricted the additive neuroprotective effect olanzapine at its higher doses.

In summary, this study provides evidence that acute administration of olanzapine by the dose range indicated protects neurons from death after permanent cerebral ischemia. This finding indicates that atypical neuroleptic agents in common with lithium and valproate may have neuroprotective actions. Further experiments to evaluate the long-term clinical reflections of such neuroprotective effects of atypical neuroleptics also in bipolar/schizophrenic patients via magnetic resonance imaging and spectroscopy studies would be the logical future steps to be taken in the field of psychiatric research.

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