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Neuroprotective effect of atypical antipsychotics in cognitive and non-cognitive behavioral impairment in animal models

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Abbreviations: Bcl-2, B cell lymphoma protein-2; BDNF, brain-derived neurotrophic factor; CPu, caudate putamen; GCI, global cerebral ischemia; METH, methamphetamine; MPP+, N-methyl-4-phenylpyridinium ion; NMDA, N-methyl-D-aspartate; OA, okadaic acid; PCP, phencyclidine; 5-HT, serotonin; SOD1, superoxide dismutase; TUNEL, terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling; TH, tyrosine hydroxylase

Key words: atypical antipsychotics, neuroprotective effect, memory, anxiety-like behavior, neurotoxicity

Antipsychotic drugs are divided into two groups: typical and atypical. Recent clinical studies show atypical antipsychotics have advantages over typical antipsychotics in a wide variety of neuropsychiatric conditions, in terms of greater efficacy for positive and negative symptoms, beneficial effects on cognitive functioning, and fewer extra pyramidal side effects in treating schizophrenia. As such, atypical antipsychotics may be effective in the treatment of depressive symptoms associated with psychotic and mood disorders, posttraumatic stress disorder and psychosis in Alzheimer disease. In this paper, we describe the effects and potential neurochemical mechanisms of action of atypical antipsychotics in several animal models showing memory impairments and/or non-cognitive behavioral changes. The data provide new insights into the mechanisms of action of atypical antipsychotics that may broaden their clinical applications.

Introduction

Schizophrenia is a severe and chronic mental illness that affects about 1% of the world’s population. Antipsychotic drugs having therapeutic efficacy in treating schizophrenia are divided into two groups: typical (conventional) and atypical (novel). Typical antipsychotics, represented by chlorpromazine and haloperidol, ameliorate only the positive symptoms. Atypical antipsychotics, including clozapine, olanzapine, quetiapine and risperidone, are effective in treating the positive, negative and cognitive symptoms, and have a low association with dyskinesia or Parkinsonism.1,5 In clinical studies, atypical antipsychotics have shown their efficacy in a wide variety of neuropsychiatric conditions and, as such, may be effective in the treatment of depressive symptoms associated with psychotic and mood disorders,6 in treating posttraumatic stress disorder,7 psychosis in Alzheimer’s disease8 as well as cognition. Olanzapine, quetiapine and risperidone have beneficial effects on neurocognitive function in patients with early psychosis,9 quetiapine also improves psychotic symptoms and cognition in Parkinson disease.10

Both typical and atypical antipsychotics can bind to dopamine receptors, and the blockade of dopamine D2 receptors in the mesolimbic region is thought to be the mechanism responsible for the reversal of positive symptoms by antipsychotics.11 Atypical antipsychotics can also bind to serotonin (5-HT) receptors. The different affinities of antipsychotics for brain dopamine D2 and 5-HT2A receptors may be helpful in understanding some of the different therapeutic effects of atypical antipsychotics;12,13 however, the mechanisms underlying their therapeutic effects on negative and cognitive symptoms of schizophrenia may be beyond the dopamine and serotonin receptor blockade effects and therefore require further investigation.

Neuroanatomical and clinical studies of schizophrenia suggest progressive neuropathological changes (such as neuronal atrophy and/or cell death) occur over the course of the disease.14-17 Cognitive deficits tend to occur early in the course of schizophrenia, and the severity of deficits is predictive of the long-term treatment outlook for patients.18 Neural injury or neurodegeneration may cause cognitive deficits in schizophrenia.19 Therefore, the beneficial effects of atypical antipsychotics on behavior may also relate to their possible effects on neuroprotection and/or neurogenesis beyond the dopamine and serotonin receptor blockade effects. In in vivo studies using rats, atypical antipsychotics attenuated the methamphetamine-induced memory impairment and neurotoxicity,20,21 alleviated theamphetamine-induced anxiety-like behavioral changes,22 counteracted the phencyclidine-induced reference memory impairment and decrease of Bcl-XL/Bax ratio in the cortex,23 and reversed the suppression of hippocampal neurogenesis caused by repeated restraint stress.24 In in vitro studies, atypical antipsychotics were effective in reducing PC12 cell death induced by serum withdrawal or by addition of hydrogen
peroxide, β-amyloid peptide, or N-methyl-4-phenylpyridinium ion (MPP+).25-28

This paper reviews the behavioral effects of atypical antipsychotics on a number of animal models relevant to schizophrenia and other neurodegenerative disorders, and explores the possible working mechanisms of atypical antipsychotics behind their beneficial behavioral effects (Table 1). To investigate the possible neuroprotective effects of atypical antipsychotics, we review animal models induced by a variety of possible neurotoxic consequences.

**Effect of Quetiapine on a Neurotoxic Regimen of Amphetamine-Induced Anxiety-Like Behavioral Change**

The most widely studied class of drug-induced models of schizophrenia is based on the behavioral effects of psychostimulant drugs, such as amphetamine. One aspect of the psychostimulant model that has generated considerable interest involves the dosage regimens required for amphetamine to produce psychotic-like behavior. Most preclinical studies show anxiogenic-like effects at low doses of amphetamine (0.5–5 mg/kg).29-32 Conversely, studies by Dawson et al. show anxiolytic-like effects of d-amphetamine (0.75, 1.5 mg/kg) in rats,33 while Lister reports no effects of d-amphetamine (1, 2 and 4 mg/kg) on anxiety-like behavior in mice.34 The long-term neurotoxic consequences of dl-amphetamine (20 mg/kg/day, 5 days) induces the decrease of striatal tyrosine hydroxylase (TH) immunostaining, and significantly reduces anxiety-like behaviors in both the light/dark box and open field tests in rats.22 Striatal TH immunoreactivity is one of the neuronal markers used to assess the integrity of dopaminergic terminals, and is decreased by toxic doses of amphetamine and amphetamine-like compounds.35,36 Structural changes, pathognomonic of neuronal damage, have been noted using histofluorescent techniques in striatal dopaminergic terminals following continuous amphetamine administration.37

Chronic administration of quetiapine normalizes both the amphetamine-induced increase in the time spent in the light box in the light/dark box test as well as the ratio of ambulation inside the inner circle over total ambulation distance (% in the open field test induced by chronic administration of dl-amphetamine (AMP, 20 mg/kg/day, five days) in rats. Results are expressed as means ± S.E.M. (n = 5 in the CON group, n = 6 in each of the other three groups). *p < 0.05 vs CON, #p < 0.05 vs AMP.

![Figure 1](image_url)

**Table 1** Effects of atypical antipsychotics on animal models relevant to schizophrenia and other neurodegenerative disorders

| Damage factors       | Impairments (Animals)                          | Clinical relevance | Atypical antipsychotics | Drug effects (Reference) |
|----------------------|------------------------------------------------|--------------------|-------------------------|--------------------------|
| Amphetamine          | Anxiety-like behavior (Rats)                  | Schizophrenia      | Quetiapine              | Attenuation (22)         |
| Methamphetamine     | Memory, Tyrosine hydroxylase in caudate putamen (Rats) | Schizophrenia      | Quetiapine              | Olanzapine               |
| Phencyclidine        | Memory, Cortex Bcl-X/-Bax ratio (Rats)        | Schizophrenia      | Quetiapine              | Attenuation (23)         |
| Okadaic acid         | Memory, Hipocampal cell death (Rats)          | Neurodegeneration   | Olanzapine              | Attenuation (99)         |
| Cerebral ischemia    | Memory, Depressive and anxiety-like behaviors, Hipocampal neurodegeneration (Mice) | Stroke             | Quetiapine              | Attenuation (122, 123)   |

Figure 1. Chronic administration of quetiapine (QUE, 10 mg/kg/day, for 33 days) normalized the increased time spent in the light box (A) in the light/dark box test and attenuated the increased ratio of ambulation inside the inner circle over the total ambulation distance (%) (B) in the open field test induced by chronic administration of dl-amphetamine (AMP, 20 mg/kg/day, five days) in rats. Results are expressed as means ± S.E.M. (n = 5 in the CON group, n = 6 in each of the other three groups). *p < 0.05 vs CON, #p < 0.05 vs AMP.

The effects of quetiapine on dopaminergic and/or 5-HT receptors and its neuroprotective effects.

The modulation effects of quetiapine on dopaminergic and/or 5-HT receptors may be involved in its therapeutic effects on the amphetamine-induced changes of anxiety-like behavior. Behavioral pharmacology experiments suggest atypical antipsychotic drugs, which are mixed dopamine D2 and 5-HT2 antagonists effective in the treatment of schizophrenia, can attenuate some behavioral effects induced by amphetamine.40-43 Animal studies show a dopaminergic mechanism is involved in the change of anxiety-like consequences of amphetamine, and that an increase in dopaminergic transmission may be responsible for its anxiogenic effect.29,32 Therefore, the effects of quetiapine on dopaminergic receptors may be involved in its therapeutic effects on amphetamine-induced changes in...
anxiety-like behavior. On the other hand, the lower affinity and faster dissociation of quetiapine for dopamine D2 receptor suggests the involvement of neurotransmitter systems other than the dopaminergic system. Among possible candidates, the 5-HT system is the most likely to be involved, as quetiapine has a high affinity for 5-HT receptors. Reports show decreased 5-HT function results in an apparent anxiolytic effect in rodents. Therefore, the effects of quetiapine on 5-HT receptors may also be involved in its therapeutic effects on amphetamine-induced changes in anxiety-like behavior.

The neuroprotective effects of quetiapine affecting dopaminergic and/or 5-HT system damage may also be involved in its therapeutic action, as evident in changes of anxiety-like behavior induced by a neurotoxic regimen of amphetamine. Chronic pre-treatment and/or post-treatment of atypical antipsychotic drugs upregulates neuroprotective proteins such as B cell lymphoma protein-2 (Bcl-2) and brain-derived neurotrophic factor (BDNF) in the brain, normalizes the stress-induced decrease of Bcl-2 and BDNF in the hippocampus, and exerts neuroprotective effects on methamphetamine-induced neurotoxicity.

In particular, quetiapine attenuates the amphetamine-induced hyperthermia shown to accompany neuronal damage produced by various amphetamine-like compounds.

**Effect of Quetiapine on Methamphetamine-Induced Memory Impairment and Neurotoxicity**

Methamphetamine (METH) is a psychomotor stimulant that can cause neuropsychiatric complications. In addition to acute neurochemical and behavioral effects, repeated moderate dose administration of this stimulant produces long-term neurotoxicity to dopaminergic and serotonergic nerve terminals, hyperthermia and high mortality. Hyperthermia accompanies the neuronal damage produced by METH. Tyrosine hydroxylase (TH) immunoreactivity in striatum, one of neuronal markers used to assess the integrity of dopaminergic terminals, is decreased by toxic doses of METH. The administration of METH also caused cognitive impairment in clinical study, and induced recognition memory impairment in rats. The METH-induced disruption of the striatal dopaminergic terminals may contribute to the object recognition impairment.

Chronic administration of quetiapine after METH injections reverses the METH-induced recognition memory impairment in an object recognition task (Fig. 2A). The object recognition task measures non-spatial memory in the rat, takes advantage of the rat’s unprompted nature to explore its surroundings, and requires the rats to recall to which of two small objects they have had prior exposure. In addition, quetiapine (Fig. 2B) and olanzapine attenuate the METH-induced dopaminergic terminal neurotoxicity, shown as a decrease of TH immunostaining in the caudate putamen (CPu) of striatum in rats. The memory improvement is parallel to the attenuating effect of quetiapine on the METH-induced neurotoxicity, suggesting an association between both the neuroprotective and memory improving effects exerted by quetiapine. The ability of quetiapine to reverse METH-induced object recognition impairment may be associated with therapeutic effects of quetiapine on METH-induced striatal neurotoxicity.

The ability of chronic administration of quetiapine to counteract METH-induced dopaminergic terminal neurotoxicity in the CPu suggests a neuroprotective action of quetiapine. METH can induce significant increases in the pro-death Bcl-2 gene family (Bad, Bax and Bid), and decreases in the anti-death genes, Bcl-2 and Bcl-X,. Bcl-2 protects METH-induced dose-dependent apoptosis in immortalized neural cells. In addition, a possible mechanism of METH neurotoxicity is the formation of reactive oxygen species and oxidative stress. The elevation of oxidizable dopamine concentrations may be primarily responsible for METH-induced dopaminergic terminal injury. Bcl-2 protects against generators of reactive oxygen species, increases antioxidant defenses, and decreases levels of reactive oxygen species and oxidative damage. Therefore, the neuroprotective effects of chronic administration of quetiapine on METH-induced neurotoxicity may involve the modulation of the Bcl-2 family, the upregulation of the neuroprotective protein, Bcl-2, and the prevention of oxidative stress and stress-related damages. Furthermore, the attenuating effect of quetiapine on METH-induced hyperthermia may be responsible for the neuroprotective effects of quetiapine. Correlating with the METH-induced decrease of striatal dopamine content and the striatal terminal degeneration, hyperthermia may play an important role in METH neurotoxicity. The critical determinant of METH-induced neurotoxicity is METH-induced hyperthermia; attenuation of the hyperthermia induced by METH affords a protective role against neurochemical depletions and striatal TH activity.
Effect of Quetiapine on Phencyclidine-Induced Memory Impairment and Neurotoxicity

Phencyclidine (PCP), an N-methyl-D-aspartate (NMDA) receptor antagonist, can cause psychoses and negative symptoms, and is used as a pharmacological model of schizophrenia.23 PCP impairs learning and memory performance in rats.23,72-74 PCP also induces neurodegeneration75-77 and apoptosis78 in rat brain, and can decrease Bcl-XL and increase Bax in the frontal cortex of perinatal rats.79 A single dose (50 mg/kg) of PCP causes reference spatial memory impairment in the radial maze task and a decrease in the ratio of Bcl-XL (an anti-apoptotic Bcl-2 family member) to Bax (a pro-apoptotic analogue) in the posterior cingulate cortex in rats.23 The Bcl-2 protein family, which contains pro- and anti-apoptotic proteins, represents some of the most well-defined regulators of the neurodegenerative process.80 The Bcl-XL/Bax ratio is an index that can determine whether an apoptotic stimulus results in the life or death of a cell.81 The PCP-induced lower ratio of Bcl-XL/Bax indicates PCP may decrease the survival of cells in the posterior cingulate cortex. The posterior cingulate plays an important role in analyzing the significance of objects within a topographical representation and in passing this representation to the hippocampal system for memory formation.82 The posterior cingulate cortex, per se, plays a role in spatial learning in animals;83 therefore, the PCP-induced reference spatial memory impairment is likely associated, at least in part, with the neurotoxicity in the posterior cingulate cortex caused by PCP.

Chronic administration of quetiapine counteracts the PCP-induced reference memory impairment in an eight-arm radial maze task and attenuates the PCP-induced decrease of the Bcl-XL/Bax ratio in the posterior cingulate cortex23 (Fig. 3). In all training trials of the radial maze task, the same four arms were baited (one bait per arm), while the other four arms were never baited. Reference memory is regarded as a long-term memory for information that remains constant over repeated trials (memory for the positions of baited arms), while working memory is considered as a short-term memory in which the information to be remembered changes in every trial (memory for the positions of arms that have already been visited in each trial).83 The memory improvement due to quetiapine is parallel to the alleviating effect of quetiapine on the PCP-induced decrease of Bcl-XL/Bax ratio in the posterior cingulate cortex, suggesting an association between both the neuroprotective and the memory improving effects exerted by quetiapine. Because evidence suggests excessive dopaminergic transmission could contribute to the PCP-induced cell injury in the brain,84,85 quetiapine may attenuate PCP-induced neurotoxicity by acting on dopamine receptors as do other antipsychotic agents, such as clozapine and olanzapine.86-88 Like olanzapine,49,50,89 the neuroprotective effects of chronic administration of quetiapine may also involve the upregulation of neuroprotective proteins such as Bcl-2 and BDNF.

Effect of Olanzapine on Okadaic Acid-Induced Memory Impairment and Hippocampal Cell Death

Okadaic acid (OA), a selective and potent inhibitor of the serine/threonine phosphatases 1 and 2A,90,91 causes neuronal cell death in vitro92 and in vivo.93,94 Infusion of OA into rat brain results in severe memory impairment, accompanied by remarkable neuropathological changes including hippocampal neurodegeneration, a paired helical filament-like phosphorylation of tau protein, and the formation of β/ A4-amyloid containing plaque-like structures in gray and white matter areas.94-98 A unilateral microinjection of OA (100 ng) into the dorsal hippocampus induces spatial working and reference memory impairment, decreases the number of the surviving pyramidal neurons in the CA1 region of the hippocampus, and causes hippocampal apoptosis, as revealed by terminal deoxynucleutidyl transferase-mediated biotinylated UTP nick end labeling (TUNEL) staining in rats.99 Because an intact hippocampus is required for recall, item recognition and associative recognition memory in animals,100,101 the OA-induced spatial memory impairment may partially be attributed to the hippocampal cell death it causes.

Chronic administration of olanzapine significantly attenuates the OA-induced spatial memory impairment (Fig. 4) in the radial arm maze task and cell death evaluated by TUNEL (Fig. 5) and Nissl staining in the hippocampus of rats.99 The neuroprotective effect on hippocampal cell death is associated with the memory improving effect exerted by olanzapine.99 The attenuating effect of olanzapine on the OA-induced neurodegeneration and apoptosis provides direct evidence supporting the neuroprotective action of olanzapine. Olanzapine can regulate the translocation and expression of pro- and anti-apoptotic proteins Bcl-XL and Bcl-2 in PC12 cells.28 In animal studies, olanzapine upregulates the expression of Bcl-2 and BDNF in the hippocampus49,89 and helps restore the repeated restraint stress-induced decrease in these two neuroprotective proteins in
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OA-induced apoptosis is associated with downregulation of Bcl-2 and can be prevented by upregulation of Bcl-2. Therefore, Bcl-2 may play an important role in the neuroprotective effects of olanzapine on OA-induced neurodegeneration and apoptosis. Olanzapine may also attenuate OA-induced neurotoxicity by upregulating superoxide dismutase105-107 and perform protective effects on OA-induced apoptotic cell death by modulating the expression of pro- and anti-apoptotic proteins, such as Bax and Bcl-X. However, further studies are necessary to elucidate whether olanzapine attenuates OA-induced neurotoxicity by directly affecting the activation of phosphatases or caspases.

OA-induced spatial memory impairment in the present paradigm is likely due to the secondary effect of OA-induced hippocampal cell death. The ability of olanzapine to improve OA-induced spatial memory impairment in rats may be subsequent to its attenuating effects on OA-induced hippocampal cell death. Olanzapine in rats induces an increase of acetylcholine release in the medial prefrontal cortex and hippocampus, a possible contributing factor to cognitive improvement in schizophrenia. Therefore, the effects of olanzapine on acetylcholine may be an additional contributor to its ability to improve OA-induced memory impairment.

**Effect of Quetiapine on Global Cerebral Ischemia-Induced Cognitive and Non-Cognitive Behavioral Impairments and Hippocampal Neurodegeneration**

Cerebral ischemia is one of the major leading causes of morbidity and mortality worldwide. Cognitive deficits, neuropsychiatric disorders and brain damages occur in global cerebral ischemia (GCI) subjects. Post-stroke depression, following cerebrovascular lesions, along with post-stroke anxiety, inhibit physical and cognitive recovery. The ischemia-induced brain damage is believed to be associated with cognitive and memory dysfunction. In animal studies, GCI induced by transient occlusion of common carotid arteries causes spatial memory impairment and hippocampal neurodegeneration, and induces changes in depressive and anxiety-like behaviors.

Our study shows the administration of quetiapine attenuates GCI-induced spatial memory impairment in a water maze test and neurodegeneration in the hilus of hippocampus in mice, suggesting quetiapine's neuroprotective effects may contribute to its beneficial effect on memory impairment. In this study, quetiapine is pre-administered two weeks before GCI, so it may act to attenuate cell death rather than “improve memory” after disease onset. Quetiapine...
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Atypical antipsychotics have an antioxidant capacity. Clozapine, olanzapine, quetiapine, and risperidone increase the gene expression of superoxide dismutase (SOD1) in PC12 cells, and prevent cell death after serum withdrawal. As such, atypical antipsychotics may have a common antioxidant action responsible for their cytoprotective effects in reducing PC12 cell death induced by serum withdrawal or by addition of hydrogen peroxide, β-amyloid peptide, or MPP+. Olanzapine and quetiapine prevent PC12 cells from Aβ-induced apoptosis and the overproduction of intracellular reactive oxygen species, attenuate Aβ-induced activity changes of the antioxidant enzymes (SOD1, catalase and glutathione peroxidase), and block Aβ-induced decrease in mitochondrial membrane potential in PC12 cells. Furthermore, atypical antipsychotics may demonstrate other aspects of neuroprotective effect. For example, the treatment effect of olanzapine may be associated with its effects on brain gray matter volume and psychopathology in schizophrenia.

Neuroprotective Mechanisms of Atypical Antipsychotics

Atypical antipsychotics upregulate the level of BDNF, an important neurotrophin mainly expressed and distributed in brain neurons. Neurotrophins are growth factors that act directly on neurons to support their growth, differentiation and survival. Chronic administration (28 days) of clozapine (10 mg/kg) and olanzapine (2.7 mg/kg) upregulates BDNF mRNA expression in the hippocampus of rats. Quetiapine attenuates the immobilization stress-induced decrease of BDNF expression in rat hippocampus and chronic administration of olanzapine accelerates the restoration of BDNF in hippocampal neurons from decrease induced by repeated restraint stress. Atypical antipsychotics also modulate the levels of other growth factors, such as fibroblast growth factor 2 (FGF-2) and nerve growth factor (NGF), that may play important roles in changing synaptic plasticity, normalizing cognitive deficits, and preventing cell degeneration.

Atypical antipsychotics upregulate the level of Bcl-2 and modulate the Bcl-XL/Bax ratio in brain. Bcl-2, a neuroprotective protein, inhibits apoptosis by sequestering proforms of death-driving caspases and preventing the release of mitochondrial apoptotic factors into the cytoplasm. The mRNA and protein expression of Bcl-2 in rat frontal cortex and hippocampus are increased after chronic atypical antipsychotic treatment. Olanzapine prevents METH-induced Bcl-2 decrease and accelerates the restoration of Bcl-2 in hippocampal neurons from the repeated restraint stress-induced decrease.

Atypical antipsychotics upregulate the level of Bcl-2 and modulate the Bcl-XL/Bax ratio in brain. Atypical antipsychotics attenuate neurotoxicity of β-amyloid by modulating Bax and Bcl-XL expression and localization in PC12 cells. In animal studies, quetiapine attenuates the phencyclidine-induced decrease in the Bcl-XL/Bax ratio in the posterior cingulate cortex in rats. Atypical antipsychotics have an antioxidant capacity. Clozapine, olanzapine, quetiapine and risperidone increase the gene expression of superoxide dismutase (SOD1) in PC12 cells, and prevent cell death after serum withdrawal. As such, atypical antipsychotics may have a common antioxidant action responsible for their cytoprotective effects in reducing PC12 cell death induced by serum withdrawal or by addition of hydrogen peroxide, β-amyloid peptide, or MPP+. Olanzapine and quetiapine prevent PC12 cells from Aβ-induced apoptosis and the overproduction of intracellular reactive oxygen species, attenuate Aβ-induced activity changes of the antioxidant enzymes (SOD1, catalase and glutathione peroxidase), and block Aβ-induced decrease in mitochondrial membrane potential in PC12 cells. Furthermore, atypical antipsychotics may demonstrate other aspects of neuroprotective effect. For example, the treatment effect of olanzapine may be associated with its effects on brain gray matter volume and psychopathology in schizophrenia.

Atypical Antipsychotics Upregulate Brain Neurogenesis

Neurogenesis (neuronal regeneration) is a process of generating functionally integrated neurons from progenitor cells. Atypical antipsychotics can increase cell proliferation and neurogenesis in adult rat brain. In addition, quetiapine reverses the suppression of hippocampal neurogenesis caused by repeated restraint stress. Although the function of neurogenesis in the hippocampus of transgenic mice under physiological or pathological conditions is unknown, new neurons from the adult human hippocampus have shown some function. The formation of some types of memory relies on the continuous production of new hippocampal neurons throughout adulthood. Therefore, the beneficial behavioral effects of atypical antipsychotics may be linked to their upregulation of neurogenesis. However, the effect of atypical antipsychotics on the hippocampal neurogenesis is still controversial. Other labs using different dosages and schedules show atypical antipsychotics have no effect on hippocampal neurogenesis (as reviewed by Newton and Duman).

Summary

Atypical antipsychotics attenuate both cognitive and non-cognitive behavioral impairments in different animal models of neurotoxicity. Their beneficial behavioral effects are not only related to their dopamine and serotonin receptor blockade effects, but also to their effects on neuroprotection, neurotrophins and neurogenesis. The neuroprotective potential of atypical antipsychotics may contribute to their therapeutic effects in treating cognitive and non-cognitive impairments in schizophrenia and other neurodegenerative diseases.

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