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Special Focus: Molecular and Cellular Events Controlling Neuronal and Brain Function and Dysfunction

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

Jue He,[1,2] Jiming Kong,[3] Qing-Rong Tan,[1*] and Xin-Min Li,[2,3,*]

[1]Department of Psychiatry, Xijing Hospital; The Fouth Military Medical University; Xi'an, China; [2]Department of Psychiatry; and [3]Department of Human Anatomy and Cell Science; Faculty of Medicine; University of Manitoba; Winnipeg, MB CA

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 deoxynucleutidyl 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 disease[8] 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 the amphetamine-induced anxiety-like behavioral changes,[22] counteracted the phencyclidine-induced reference memory impairment and decrease of Bcl-X_L/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

*Correspondence to: Xin-Min Li; Department of Psychiatry; Faculty of Medicine; University of Manitoba; PZ432-771 Bannatyne Avenue; Winnipeg, MB R3E 3N4 CA; Email: xinmin_li@umanitoba.ca or Qing–Rong Tan, Email: tanqingrong@gmail.com

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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	Attenuation (20, 21)
Phencyclidine	Memory, Cortex Bcl-X_L/Bax ratio (Rats)	Schizophrenia	Quetiapine	Attenuation (23)
Okadaic acid	Memory, Hippocampal cell death (Rats)	Neurodegeneration	Olanzapine	Attenuation (99)
Cerebral ischemia	Memory, Depressive and anxiety-like behaviors, Hippocampal neurodegeneration (Mice)	Stroke	Quetiapine	Attenuation (122, 123)

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 to total ambulation in the open field test in rats (Fig. 1).[22] This suggests therapeutic effects of quetiapine on amphetamine-induced anxiety-like behavioral changes. Clearly, this finding has clinical relevance, recognizing the abuse potential of amphetamine and its capacity for exacerbating or inducing mood and psychiatric disturbances in humans.[38,39] Quetiapine's mechanism of effect on amphetamine-induced anxiety-like behavioral changes may be related to its effect on dopaminergic and/or 5-HT receptors and its neuroprotective effects.

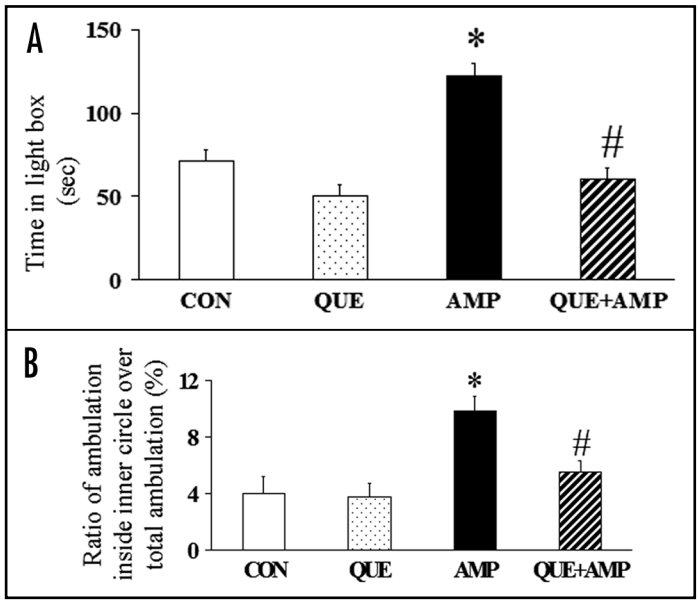

Figure 1. Chronic administration of quetiapine (QUE, 10 mg/kg/day, for 33 days) normalized the increased time spent in the light box (A) in the light/dark box test and attenuated the increased ratio of ambulation distance inside the inner circle over the total ambulation distance (%) (B) in the open 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 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

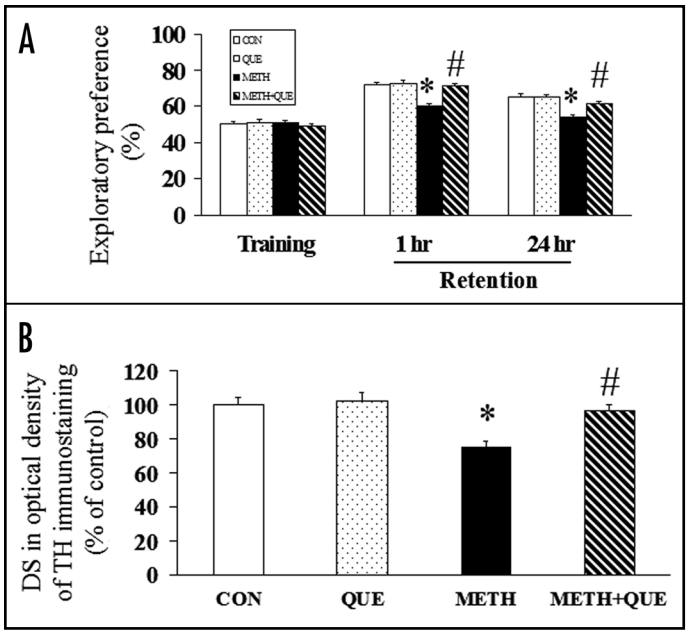

Figure 2. (A) METH (5 mg/kg x 4, 2 hr intervals) and chronic administration of quetiapine (QUE, 10 mg/kg/day, 28 days) had no effect on the exploratory preference during the training session; chronic administration of quetiapine reversed the METH-induced decrease of exploratory preference in rats during the retention session (1 hr and 24 hr) of the object recognition task (n = 8 in CON and QUE, n = 11 in METH and METH + QUE). (B) Chronic administration of quetiapine (10 mg/kg/day, 28 days) reversed the METH (5 mg/kg x 4, 2 hr intervals)-induced decrease of DS (difference score) in optical density of TH immunostaining in the caudate putamen of rats (n = 4 in CON and QUE, n = 5 in METH and METH + QUE). Rats were sacrificed 24 hr after the object recognition task. Results are expressed as means ± S.E.M. *$p < 0.05$ vs CON, #$p < 0.05$ vs METH.

anxiety-like behavior. On the other hand, the lower affinity and faster dissociation of quetiapine for dopamine D2 receptor[44] 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.[45] Reports show decreased 5-HT function results in an apparent anxiolytic effect in rodents.[46-48] 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.[20,49-51] In particular, quetiapine attenuates the amphetamine-induced hyperthermia[22] shown to accompany neuronal damage produced by various amphetamine-like compounds.[52-56]

Effect of Quetiapine on Methamphetamine-Induced Memory Impairment and Neurotoxicity

Methamphetamine (METH) is a psychomotor stimulant that can cause neuropsychiatric complications.[57] 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.[58-60] Hyperthermia accompanies the neuronal damage produced by METH.[52,53] 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.[35,36] The administration of METH also caused cognitive impairment in clinical study,[61] and induced recognition memory impairment in rats.[62,63] The METH-induced disruption of the striatal dopaminergic terminals may contribute to the object recognition impairment.[63]

Chronic administration of quetiapine after METH injections reverses the METH-induced recognition memory impairment in an object recognition task[21] (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.[21] 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.[20,21] 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.[21]

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_L.[64] Bcl-2 protects METH-induced dose-dependent apoptosis in immortalized neural cells.[65] In addition, a possible mechanism of METH neurotoxicity is the formation of reactive oxygen species and oxidative stress.[66] The elevation of oxidizable dopamine concentrations may be primarily responsible for METH-induced dopaminergic terminal injury.[60] Bcl-2 protects against generators of reactive oxygen species, increases antioxidant defenses, and decreases levels of reactive oxygen species and oxidative damage.[67] Therefore, the neuroprotective effects of chronic administration of quetiapine on METH-induced neurotoxicity may involve the modulation of the Bcl-2 family,[23,28] the upregulation of the neuroprotective protein, Bcl-2,[20,49,50] and the prevention of oxidative stress and stress-related damages.[68] Furthermore, the attenuating effect of quetiapine on METH-induced hyperthermia may be responsible for the neuroprotective effects of quetiapine.[20,22] Correlating with the METH-induced decrease of striatal dopamine content and the striatal terminal degeneration, hyperthermia may play an important role in METH neurotoxicity.[52,69] The critical determinant of METH-induced neurotoxicity is METH-induced hyperthermia;[70] attenuation of the hyperthermia induced by METH affords a protective role against neurochemical depletions and striatal TH activity.[53]

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.[71] PCP impairs learning and memory performance in rats.[23,72-74] PCP also induces neurodegeneration[75-77] and apoptosis[78] in rat brain, and can decrease Bcl-X_L 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-X_L (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-X_L/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-X_L/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-X_L/Bax ratio in the posterior cingulate cortex[23] (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).[23] The memory improvement due to quetiapine is parallel to the alleviating effect of quetiapine on the PCP-induced decrease of Bcl-X_L/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.

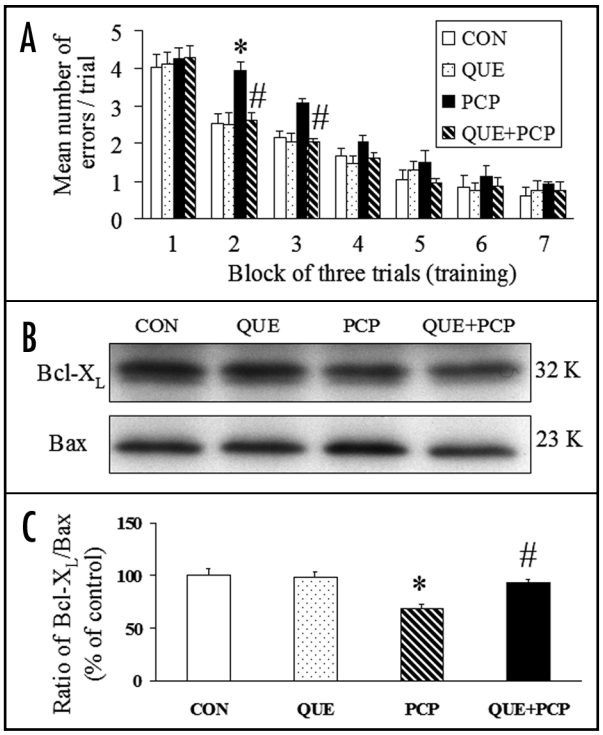

Figure 3. (A) Chronic administration of quetiapine (QUE, 10 mg/kg/day, 16 days) counteracted the PCP (50 mg/kg)-induced spatial reference memory formation impairment of rats in the radial arm maze task. (B) Representative western blot bands of Bcl-X_L and Bax in the posterior cingulate cortex of rats. (C) Chronic administration of quetiapine (10 mg/kg/day, 16 days) counteracted the PCP (50 mg/kg)-induced decrease of Bcl-X_L/Bax ratio in the posterior cingulate cortex. Results are expressed as means ± S.E.M. (n = 6–8 in each group). *$p < 0.05$ vs CON, #$p < 0.05$ vs PCP.

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 vitro[92] 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-X_L and Bcl-2 in PC12 cells.[28] In animal studies, olanzapine upregulates the expression of Bcl-2 and BDNF in the hippocampus[49,89] and helps restore the repeated restraint stress-induced decrease in these two neuroprotective proteins in

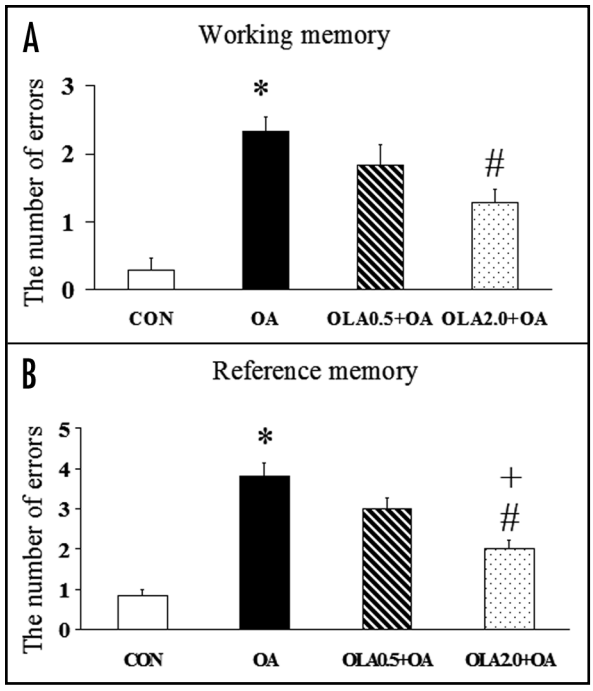

Figure 4. Olanzapine (OLA) significantly attenuated the OA-induced impairment in working (A) and reference (B) memory measured by the radial arm maze task 1 week after the microinjection of OA or saline into the right hippocampus of rats. Olanzapine did not affect the spatial working and reference memory formation before OA or saline microinjection. Results are expressed as means ± S.E.M. (n = 6–7 in each group). *p < 0.05 vs CON, #p < 0.05 vs OA and +p < 0.05 vs OLA0.5 + OA.

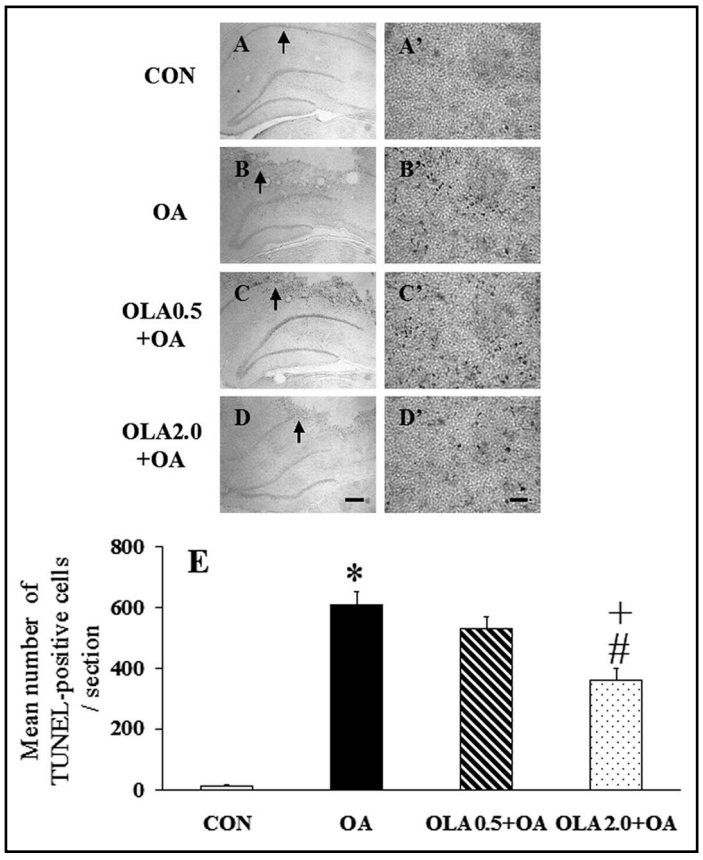

Figure 5. (A–D, A′–D′) Representative photomicrographs of TUNEL staining in the injected hippocampus of rats in the CON (A and A′), OA (B and B′), OLA0.5 + OA (C and C′) and OLA2.0 + OA (D and D′) groups. The high magnification of right photomicrographs (A′–D′) are enlargement of selected sections of (A–D), respectively. Arrows on the low magnification panels indicate the location of the high magnification images. In the hippocampi of OA-injected groups (B, B′; C, C′; and D, D′), the TUNEL-positive cells are visible in different frequency, whereas almost no TUNEL-positive cells are evident in the hippocampus of the control group (A and A′). The scale bar represents 300 μm in (A–D) and 30 μm in (A′–D′). (E) Quantitative analysis of the effect of olanzapine on the OA-induced increase of TUNEL-positive cells in the injected hippocampus. The number of TUNEL-positive cells in the hippocampus was counted at 400x magnification. Results are expressed as means ± S.E.M. (n = 6–7 in each group). *p < 0.05 vs CON, #p < 0.01 vs OA and +p <0 .05 vs OLA0.5 + OA.

hippocampal neurons.[50] OA-induced apoptosis is associated with downregulation of Bcl-2 and can be prevented by upregulation of Bcl-2.[102-104] 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 dismutase[105-107] 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_L.[28,103] 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.[94] 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.[99] 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.[108,109] 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.[110-113] Post-stroke depression, following cerebrovascular lesions, along with post-stroke anxiety, inhibit physical and cognitive recovery.[112-117] The ischemia-induced brain damage is believed to be associated with cognitive and memory dysfunction.[114,115,118-120] 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.[121-123]

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.[122] In this study, quetiapine is pre-administrated two weeks before GCI, so it may act to attenuate cell death rather than "improve memory" after disease onset. Quetiapine

may attenuate GCI-induced neurotoxicity by upregulating neuroprotective proteins or regulating NMDA receptors, thus leading to the downregulation of oxidative stress.[122]

Quetiapine effectively attenuates GCI-induced changes in depressive and anxiety-like behaviors in mice.[123] Dysfunction of neurotransmitter systems is the major cause of the depressive-like behavior in ischemic mice, and these depressive-like behaviors are relevant to the low levels of norepinephrine and dopamine.[124] Serotonin deficiency is also postulated to be relevant to the pathophysiology of depression after stroke.[125,126] In addition, GCI-induced injury of dopaminergic and serotoninergic systems in mice may cause anxiety-like behavioral changes;[123] therefore, the neuroprotective effects of quetiapine on dopaminergic and serotoninergic system damage may be involved in its action to regulate the depressive- and anxiety-like behaviors. In fact, quetiapine can alleviate the GCI-induced neurodegeneration and neuron loss as well as attenuate the GCI-induced decrease of striatal TH immunostaining.[122,123]

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.[127] Chronic administration (28 days) of clozapine (10 mg/kg) and olanzapine (2.7 mg/kg) upregulates BDNF mRNA expression in the hippocampus of rats.[89] Quetiapine attenuates the immobilization stress-induced decrease of BDNF expression in rat hippocampus[51] and chronic administration of olanzapine accelerates the restoration of BDNF in hippocampal neurons from decrease induced by repeated restraint stress.[50] 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.[128,129]

Atypical antipsychotics upregulate the level of Bcl-2 and modulate the Bcl-X_L/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.[49,80,130] The mRNA and protein expression of Bcl-2 in rat frontal cortex and hippocampus are increased after chronic atypical antipsychotic treatment.[49] Olanzapine prevents METH-induced Bcl-2 decrease and accelerates the restoration of Bcl-2 in hippocampal neurons from the repeated restraint stress-induced decrease.[20,50] Atypical antipsychotics attenuate neurotoxicity of β-amyloid by modulating Bax and Bcl-$X_{L/S}$ expression and localization in PC12 cells.[28] In animal studies, quetiapine attenuates the phencyclidine-induced decrease in the Bcl-X_L/Bax ratio in the posterior cingulate cortex in rats.[23]

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.[25,106] 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^+.[25-28] 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.[68] 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.[131]

Atypical Antipsychotics Upregulate Brain Neurogenesis

Neurogenesis (neuronal regeneration) is a process of generating functionally integrated neurons from progenitor cells.[132] Atypical antipsychotics can increase cell proliferation and neurogenesis in adult rat brain.[133,134] In addition, quetiapine reverses the suppression of hippocampal neurogenesis caused by repeated restraint stress.[24] 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.[135] The formation of some types of memory relies on the continuous production of new hippocampal neurons throughout adulthood.[136] 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[137]).

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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References

1. Velligan DI, Newcomer J, Pultz J, Csernansky J, Hoff AL, Mahurin R, et al. Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophr Res 2002; 53:239-48.
2. Purdon SE, Malla A, Labelle A, Lit W. Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. J Psychiatry Neurosci 2001; 26:137-49.
3. Beasley CM Jr, Tollefson GD, Tran PV. Efficacy of olanzapine: An overview of pivotal clinical trials. J Clin Psychiatry 1997; 58:7-12.
4. Cuesta MJ, Peralta V, Zarzuela A. Effects of olanzapine and other antipsychotics on cognitive function in chronic schizophrenia: A longitudinal study. Schizophr Res 2001; 48:17-28.
5. Jann MW. Implications for atypical antipsychotics in the treatment of schizophrenia: Neurocognition effects and a neuroprotective hypothesis. Pharmacotherapy 2004; 24:1759-83.
6. Brugue E, Vieta E. Atypical antipsychotics in bipolar depression: Neurobiological basis and clinical implications. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31:275-82.

7. Pae CU, Lim HK, Peindl K, Ajwani N, Serretti A, Patkar AA, et al. The atypical antipsychotics olanzapine and risperidone in the treatment of posttraumatic stress disorder: A meta-analysis of randomized, double-blind, placebo-controlled clinical trials. Int Clin Psychopharmacol 2008; 23:1-8.
8. Madhusoodanan S, Shah P, Brenner R, Gupta S. Pharmacological treatment of the psychosis of alzheimer's disease: What is the best approach? CNS Drugs 2007; 21:101-15.
9. Keefe RS, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP, et al. Effects of olanzapine, quetiapine and risperidone on neurocognitive function in early psychosis: A randomized, double-blind 52-week comparison. Am J Psychiatry 2007; 164:1061-71.
10. Juncos JL, Roberts VJ, Evatt ML, Jewart RD, Wood CD, Potter LS, et al. Quetiapine improves psychotic symptoms and cognition in parkinson's disease. Mov Disord 2004; 19:29-35.
11. Wong AH, Van Tol HH. Schizophrenia: From phenomenology to neurobiology. Neurosci Biobehav Rev 2003; 27:269-306.
12. Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone and olanzapine in schizophrenia. Am J Psychiatry 1999; 156:286-93.
13. Seeman P, Tallerico T. Rapid release of antipsychotic drugs from dopamine D2 receptors: An explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. Am J Psychiatry 1999; 156:876-84.
14. Woods BT, Yurgelun-Todd D, Benes FM, Frankenburg FR, Pope HG Jr, McSparren J. Progressive ventricular enlargement in schizophrenia: Comparison to bipolar affective disorder and correlation with clinical course. Biol Psychiatry 1990; 27:341-52.
15. Waddington JL, O'Callaghan E, Buckley P, Larkin C, Redmond O, Stack J, et al. The age dependencies of MRI abnormalities in schizophrenia suggest early ventricular enlargement but later prominence of cortical atrophy. Schizophr Res 1991; 5:188-9.
16. DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R. Schizophrenia as a chronic active brain process: A study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res 1997; 74:129-40.
17. Arnold SE, Trojanowski JQ. Recent advances in defining the neuropathology of schizophrenia. Acta Neuropathol 1996; 92:217-31.
18. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996; 153:321-30.
19. Harvey PD. Comprehensive clinical psychology. In: Bellack AS, Hersen M, eds. Schizophrenia and related disorders in late life. Amsterdam: Elsevier 1998; 74-86.
20. He J, Xu H, Yang Y, Zhang X, Li XM. Neuroprotective effects of olanzapine on methamphetamine-induced neurotoxicity are associated with an inhibition of hyperthermia and prevention of bcl-2 decrease in rats. Brain Res 2004; 1018:186-92.
21. He J, Yang Y, Yu Y, Li X, Li XM. The effects of chronic administration of quetiapine on the methamphetamine-induced recognition memory impairment and dopaminergic terminal deficit in rats. Behav Brain Res 2006; 172:39-45.
22. He J, Xu H, Yang Y, Zhang X, Li XM. Chronic administration of quetiapine alleviates the anxiety-like behavioural changes induced by a neurotoxic regimen of dl-amphetamine in rats. Behav Brain Res 2005; 160:178-87.
23. He J, Xu H, Yang Y, Rajakumar D, Li X, Li XM. The effects of chronic administration of quetiapine on the phencyclidine-induced reference memory impairment and decrease of bcl-X_L/Bax ratio in the posterior cingulate cortex in rats. Behav Brain Res 2006; 168:236-42.
24. Luo C, Xu H, Li XM. Quetiapine reverses the suppression of hippocampal neurogenesis caused by repeated restraint stress. Brain Res 2005; 1063:32-9.
25. Bai O, Wei Z, Lu W, Bowen R, Keegan D, Li XM. Protective effects of atypical antipsychotic drugs on PC12 cells after serum withdrawal. J Neurosci Res 2002; 69:278-83.
26. Qing H, Xu H, Wei Z, Gibson K, Li XM. The ability of atypical antipsychotic drugs vs. haloperidol to protect PC12 cells against MPP^+-induced apoptosis. Eur J Neurosci 2003; 17:1563-70.
27. Wei Z, Bai O, Richardson JS, Mousseau DD, Li XM. Olanzapine protects PC12 cells from oxidative stress induced by hydrogen peroxide. J Neurosci Res 2003; 73:364-8.
28. Wei Z, Mousseau DD, Richardson JS, Dyck LE, Li XM. Atypical antipsychotics attenuate neurotoxicity of beta-amyloid(25-35) by modulating bax and bcl-X(l/s) expression and localization. J Neurosci Res 2003; 74:942-7.
29. Cancela LM, Basso AM, Martijena ID, Capriles NR, Molina VA. A dopaminergic mechanism is involved in the 'anxiogenic-like' response induced by chronic amphetamine treatment: A behavioral and neurochemical study. Brain Res 2001; 909:179-86.
30. Lapin IP. Anxiogenic effect of phenylethylamine and amphetamine in the elevated plus-maze in mice and its attenuation by ethanol. Pharmacol Biochem Behav 1993; 44:241-3.
31. Lin HQ, Burden PM, Christie MJ, Johnston GA. The anxiogenic-like and anxiolytic-like effects of MDMA on mice in the elevated plus-maze: A comparison with amphetamine. Pharmacol Biochem Behav 1999; 62:403-8.
32. Simon P, Panissaud C, Costentin J. Anxiogenic-like effects induced by stimulation of dopamine receptors. Pharmacol Biochem Behav 1993; 45:685-90.
33. Dawson GR, Crawford SP, Collinson N, Iversen SD, Tricklebank MD. Evidence that the anxiolytic-like effects of chlordiazepoxide on the elevated plus maze are confounded by increases in locomotor activity. Psychopharmacology (Berl) 1995; 118:316-23.
34. Lister RG. The use of a plus-maze to measure anxiety in the mouse. Psychopharmacology (Berl) 1987; 92:180-5.
35. Abekawa T, Ohmori T, Koyama T. Tolerance to the neurotoxic effect of methamphetamine in rats behaviorally sensitized to methamphetamine or amphetamine. Brain Res 1997; 767:34-44.
36. Eisch AJ, Marshall JF. Methamphetamine neurotoxicity: Dissociation of striatal dopamine terminal damage from parietal cortical cell body injury. Synapse 1998; 30:433-45.
37. Ellison G, Eison MS, Huberman HS, Daniel F. Long-term changes in dopaminergic innervation of caudate nucleus after continuous amphetamine administration. Science 1978; 201:276-8.
38. Angrist BM, Gershon S. The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. Biol Psychiatry 1970; 2:95-107.
39. Angrist B, Sathananthan G, Wilk S, Gershon S. Amphetamine psychosis: Behavioral and biochemical aspects. J Psychiatr Res 1974; 11:13-23.
40. Fulton B, Goa KL. Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. Drugs 1997; 53:281-98.
41. Grant S, Fitton A. Risperidone. A review of its pharmacology and therapeutic potential in the treatment of schizophrenia. Drugs 1994; 48:253-73.
42. Mechanic JA, Wasielewski JA, Carl KL, Holloway FA. Attenuation of the amphetamine discriminative cue in rats with the atypical antipsychotic olanzapine. Pharmacol Biochem Behav 2002; 72:767-77.
43. Rush CR, Stoops WW, Hays LR, Glaser PE, Hays LS. Risperidone attenuates the discriminative-stimulus effects of d-amphetamine in humans. J Pharmacol Exp Ther 2003; 306:195-204.
44. Kapur S, Seeman P. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. implications for atypical antipsychotic action. J Psychiatry Neurosci 2000; 25:161-6.
45. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. Life Sci 2000; 68:29-39.
46. Briley M, Chopin P, Moret C. Effect of serotonergic lesion on "anxious" behaviour measured in the elevated plus-maze test in the rat. Psychopharmacology (Berl) 1990; 101:187-9.
47. Tye NC, Everitt BJ, Iversen SD. 5-hydroxytryptamine and punishment. Nature 1977; 268:741-3.
48. Tye NC, Iversen SD, Green AR. The effects of benzodiazepines and serotonergic manipulations on punished responding. Neuropharmacology 1979; 18:689-95.
49. Bai O, Zhang H, Li XM. Antipsychotic drugs clozapine and olanzapine upregulate bcl-2 mRNA and protein in rat frontal cortex and hippocampus. Brain Res 2004; 1010:81-6.
50. Luo C, Xu H, Li XM. Post-stress changes in BDNF and bcl-2 immunoreactivities in hippocampal neurons: Effect of chronic administration of olanzapine. Brain Res 2004; 1025:194-202.
51. Xu H, Qing H, Lu W, Keegan D, Richardson JS, Chlan-Fourney J, et al. Quetiapine attenuates the immobilization stress-induced decrease of brain-derived neurotrophic factor expression in rat hippocampus. Neurosci Lett 2002; 321:65-8.
52. Albers DS, Sonsalla PK. Methamphetamine-induced hyperthermia and dopaminergic neurotoxicity in mice: Pharmacological profile of protective and nonprotective agents. J Pharmacol Exp Ther 1995; 275:1104-14.
53. Bowyer JF, Davies DL, Schmued L, Broening HW, Newport GD, Slikker W Jr, et al. Further studies of the role of hyperthermia in methamphetamine neurotoxicity. J Pharmacol Exp Ther 1994; 268:1571-80.
54. Farfel GM, Seiden LS. Role of hypothermia in the mechanism of protection against serotonergic toxicity I. experiments using 3,4-methylenedioxymethamphetamine, dizocilpine, CGS 19755 and NBQX. J Pharmacol Exp Ther 1995; 272:860-7.
55. Miller DB, O'Callaghan JP. Environment-, drug- and stress-induced alterations in body temperature affect the neurotoxicity of substituted amphetamines in the C57BL/6J mouse. J Pharmacol Exp Ther 1994; 270:752-60.
56. Schmidt CJ, Black CK, Abbate GM, Taylor VL. Methylenedioxymethamphetamine-induced hyperthermia and neurotoxicity are independently mediated by 5-HT2 receptors. Brain Res 1990; 529:85-90.
57. Lan KC, Lin YF, Yu FC, Lin CS, Chu P. Clinical manifestations and prognostic features of acute methamphetamine intoxication. J Formos Med Assoc 1998; 97:528-33.
58. O'Dell SJ, Weihmuller FB, Marshall JF. Multiple methamphetamine injections induce marked increases in extracellular striatal dopamine which correlate with subsequent neurotoxicity. Brain Res 1991; 564:256-60.
59. Wallace TL, Gudelsky GA, Vorhees CV. Methamphetamine-induced neurotoxicity alters locomotor activity, stereotypic behavior and stimulated dopamine release in the rat. J Neurosci 1999; 19:9141-8.
60. Davidson C, Gow AJ, Lee TH, Ellinwood EH. Methamphetamine neurotoxicity: Necrotic and apoptotic mechanisms and relevance to human abuse and treatment. Brain Res Brain Res Rev 2001; 36:1-22.
61. Simon SL, Domier C, Carnell J, Brethen P, Rawson R, Ling W. Cognitive impairment in individuals currently using methamphetamine. Am J Addict 2000; 9:222-31.
62. Bisagno V, Ferguson D, Luine VN. Short toxic methamphetamine schedule impairs object recognition task in male rats. Brain Res 2002; 940:95-101.
63. Schroder N, O'Dell SJ, Marshall JF. Neurotoxic methamphetamine regimen severely impairs recognition memory in rats. Synapse 2003; 49:89-96.
64. Jayanthi S, Deng X, Bordelon M, McCoy MT, Cadet JL. Methamphetamine causes differential regulation of pro-death and anti-death bcl-2 genes in the mouse neocortex. FASEB J 2001; 15:1745-52.

65. Cadet JL, Ordonez SV, Ordonez JV. Methamphetamine induces apoptosis in immortalized neural cells: Protection by the proto-oncogene, bcl-2. Synapse 1997; 25:176-84.
66. Kita T, Wagner GC, Nakashima T. Current research on methamphetamine-induced neurotoxicity: Animal models of monoamine disruption. J Pharmacol Sci 2003; 92:178-95.
67. Howard S, Bottino C, Brooke S, Cheng E, Giffard RG, Sapolsky R. Neuroprotective effects of bcl-2 overexpression in hippocampal cultures: Interactions with pathways of oxidative damage. J Neurochem 2002; 83:914-23.
68. Wang H, Xu H, Dyck LE, Li XM. Olanzapine and quetiapine protect PC12 cells from beta-amyloid peptide(25-35)-induced oxidative stress and the ensuing apoptosis. J Neurosci Res 2005; 81:572-80.
69. Bowyer JF, Tank AW, Newport GD, Slikker W Jr, Ali SF, Holson RR. The influence of environmental temperature on the transient effects of methamphetamine on dopamine levels and dopamine release in rat striatum. J Pharmacol Exp Ther 1992; 260:817-24.
70. Fukumura M, Cappon GD, Pu C, Broening HW, Vorhees CV. A single dose model of methamphetamine-induced neurotoxicity in rats: Effects on neostriatal monoamines and glial fibrillary acidic protein. Brain Res 1998; 806:1-7.
71. Javitt DC. Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia. Hillside J Clin Psychiatry 1987; 9:12-35.
72. Campbell UC, Lalwani K, Hernandez L, Kinney GG, Conn PJ, Bristow LJ. The mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) potentiates PCP-induced cognitive deficits in rats. Psychopharmacology (Berl) 2004; 175:310-8.
73. Handelmann GE, Contreras PC, O'Donohue TL. Selective memory impairment by phencyclidine in rats. Eur J Pharmacol 1987; 140:69-73.
74. Kesner RP, Dakis M, Bolland BL. Phencyclidine disrupts long- but not short-term memory within a spatial learning task. Psychopharmacology (Berl) 1993; 111:85-90.
75. Corso TD, Sesma MA, Tenkova TI, Der TC, Wozniak DF, Farber NB, et al. Multifocal brain damage induced by phencyclidine is augmented by pilocarpine. Brain Res 1997; 752:1-14.
76. Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 1989; 244:1360-2.
77. Sharp FR, Butman M, Koistinaho J, Aardalen K, Nakki R, Massa SM, et al. Phencyclidine induction of the hsp 70 stress gene in injured pyramidal neurons is mediated via multiple receptors and voltage gated calcium channels. Neuroscience 1994; 62:1079-92.
78. Mitchell IJ, Cooper AJ, Griffiths MR, Barber DJ. Phencyclidine and corticosteroids induce apoptosis of a subpopulation of striatal neurons: A neural substrate for psychosis? Neuroscience 1998; 84:489-501.
79. Wang C, McInnis J, Ross-Sanchez M, Shinnick-Gallagher P, Wiley JL, Johnson KM. Long-term behavioral and neurodegenerative effects of perinatal phencyclidine administration: Implications for schizophrenia. Neuroscience 2001; 107:535-50.
80. Adams JM, Cory S. The bcl-2 protein family: Arbiters of cell survival. Science 1998; 281:1322-6.
81. Wang C, Kaufmann JA, Sanchez-Ross MG, Johnson KM. Mechanisms of N-methyl-D-aspartate-induced apoptosis in phencyclidine-treated cultured forebrain neurons. J Pharmacol Exp Ther 2000; 294:287-95.
82. Pandya DN, Yeterian EH. Proposed neural circuitry for spatial memory in the primate brain. Neuropsychologia 1984; 22:109-22.
83. Sutherland RJ, Whishaw IQ, Kolb B. Contributions of cingulate cortex to two forms of spatial learning and memory. J Neurosci 1988; 8:1863-72.
84. Griffiths MR, Cooper AJ, Barber DJ, Mitchell IJ. Pharmacological mechanisms mediating phencyclidine-induced apoptosis of striatopallidal neurons: The roles of glutamate, dopamine, acetylcholine and corticosteroids. Brain Res 2000; 855:1-10.
85. Hertel P, Mathe JM, Nomikos GG, Iurlo M, Mathe AA, Svensson TH. Effects of D-amphetamine and phencyclidine on behavior and extracellular concentrations of neurotensin and dopamine in the ventral striatum and the medial prefrontal cortex of the rat. Behav Brain Res 1995; 72:103-14.
86. Farber NB, Price MT, Labruyere J, Nemnich J, St. Peter H, Wozniak DF, et al. Antipsychotic drugs block phencyclidine receptor-mediated neurotoxicity. Biol Psychiatry 1993; 34:119-21.
87. Olney JW, Farber NB. Efficacy of clozapine compared with other antipsychotics in preventing NMDA-antagonist neurotoxicity. J Clin Psychiatry 1994; 55:43-6.
88. Seeman P. Atypical antipsychotics: Mechanism of action. Can J Psychiatry 2002; 47:27-38.
89. Bai O, Chlan-Fourney J, Bowen R, Keegan D, Li XM. Expression of brain-derived neurotrophic factor mRNA in rat hippocampus after treatment with antipsychotic drugs. J Neurosci Res 2003; 71:127-31.
90. Ishihara H, Martin BL, Brautigan DL, Karaki H, Ozaki H, Kato Y, et al. Calyculin A and okadaic acid: Inhibitors of protein phosphatase activity. Biochem Biophys Res Commun 1989; 159:871-7.
91. Cohen P, Holmes CF, Tsukitani Y. Okadaic acid: A new probe for the study of cellular regulation. Trends Biochem Sci 1990; 15:98-102.
92. Cagnoli CM, Kharlamov E, Atabay C, Uz T, Manev H. Apoptosis induced in neuronal cultures by either the phosphatase inhibitor okadaic acid or the kinase inhibitor staurosporine is attenuated by isoquinolinesulfonamides H-7, H-8 and H-9. J Mol Neurosci 1996; 7:65-76.
93. Van Dam AM, Bol JG, Binnekade R, van Muiswinkel FL. Acute or chronic administration of okadaic acid to rats induces brain damage rather than alzheimer-like neuropathology. Neuroscience 1998; 85:1333-5.
94. He J, Yamada K, Zou LB, Nabeshima T. Spatial memory deficit and neurodegeneration induced by the direct injection of okadaic acid into the hippocampus in rats. J Neural Transm 2001; 108:1435-43.
95. Arendt T, Holzer M, Fruth R, Bruckner MK, Gartner U. Phosphorylation of tau, abeta-formation, and apoptosis after in vivo inhibition of PP-1 and PP-2A. Neurobiol Aging 1998; 19:3-13.
96. Arendt T, Holzer M, Fruth R, Bruckner MK, Gartner U. Paired helical filament-like phosphorylation of tau, deposition of beta/A4-amyloid and memory impairment in rat induced by chronic inhibition of phosphatase 1 and 2A. Neuroscience 1995; 69:691-8.
97. Zhao W, Bennett P, Sedman GL, NG KT. The impairment of long-term memory formation by the phosphatase inhibitor okadaic acid. Brain Res Bull 1995; 36:557-61.
98. Tian Q, Lin ZQ, Wang XC, Chen J, Wang Q, Gong CX, et al. Injection of okadaic acid into the meynert nucleus basalis of rat brain induces decreased acetylcholine level and spatial memory deficit. Neuroscience 2004; 126:277-84.
99. He J, Yang Y, Xu H, Zhang X, Li XM. Olanzapine attenuates the okadaic acid-induced spatial memory impairment and hippocampal cell death in rats. Neuropsychopharmacology 2005; 30:1511-20.
100. Sweatt JD. Hippocampal function in cognition. Psychopharmacology (Berl) 2004; 174:99-110.
101. Alvarado MC, Bachevalier J. Selective neurotoxic damage to the hippocampal formation impairs performance of the transverse patterning and location memory tasks in rhesus macaques. Hippocampus 2005; 15:118-31.
102. Benito A, Lerga A, Silva M, Leon J, Fernandez-Luna JL. Apoptosis of human myeloid leukemia cells induced by an inhibitor of protein phosphatases (okadaic acid) is prevented by bcl-2 and bcl-X(L). Leukemia 1997; 11:940-4.
103. Cabado AG, Leira F, Vieytes MR, Vieites JM, Botana LM. Cytoskeletal disruption is the key factor that triggers apoptosis in okadaic acid-treated neuroblastoma cells. Arch Toxicol 2004; 78:74-85.
104. Nuydens R, Dispersyn G, Van Den Keiboom G, de Jong M, Connors R, Ramaekers F, et al. Bcl-2 protects against apoptosis-related microtubule alterations in neuronal cells. Apoptosis 2000; 5:43-51.
105. Manna SK, Zhang HJ, Yan T, Oberley LW, Aggarwal BB. Overexpression of manganese superoxide dismutase suppresses tumor necrosis factor-induced apoptosis and activation of nuclear transcription factor-kappaB and activated protein-1. J Biol Chem 1998; 273:13245-54.
106. Li XM, Chlan-Fourney J, Juorio AV, Bennett VL, Shrikhande S, Keegan DL, et al. Differential effects of olanzapine on the gene expression of superoxide dismutase and the low affinity nerve growth factor receptor. J Neurosci Res 1999; 56:72-5.
107. Matias WG, Traore A, Bonini M, Sanni A, Creppy EE. Oxygen reactive radicals production in cell culture by okadaic acid and their implication in protein synthesis inhibition. Hum Exp Toxicol 1999; 18:634-9.
108. Ichikawa J, Dai J, O'Laughlin IA, Fowler WL, Meltzer HY. Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens or striatum. Neuropsychopharmacology 2002; 26:325-39.
109. Shirazi-Southall S, Rodriguez DE, Nomikos GG. Effects of typical and atypical antipsychotics and receptor selective compounds on acetylcholine efflux in the hippocampus of the rat. Neuropsychopharmacology 2002; 26:583-94.
110. Kurz AF. Uncommon neurodegenerative causes of dementia. Int Psychogeriatr 2005; 17:35-49.
111. Nunn JA, LePeillet E, Netto CA, Hodges H, Gray JA, Meldrum BS. Global ischaemia: Hippocampal pathology and spatial deficits in the water maze. Behav Brain Res 1994; 62:41-54.
112. Chemerinski E, Levine SR. Neuropsychiatric disorders following vascular brain injury. Mt Sinai J Med 2006; 73:1006-14.
113. Williams LS, Ghose SS, Swindle RW. Depression and other mental health diagnoses increase mortality risk after ischemic stroke. Am J Psychiatry 2004; 161:1090-5.
114. Bokura H, Robinson RG. Long-term cognitive impairment associated with caudate stroke. Stroke 1997; 28:970-5.
115. Bradvik B, Sonesson B, Holtas S. Spatial impairment following right hemisphere transient ischaemic attacks in patients without carotid artery stenosis. Acta Neurol Scand 1989; 80:411-8.
116. Desmond DW, Moroney JT, Sano M, Stern Y. Incidence of dementia after ischemic stroke: Results of a longitudinal study. Stroke 2002; 33:2254-60.
117. Desmond DW, Moroney JT, Sano M, Stern Y. Mortality in patients with dementia after ischemic stroke. Neurology 2002; 59:537-43.
118. Martin LJ. Neuronal cell death in nervous system development, disease and injury (review). Int J Mol Med 2001; 7:455-78.
119. Caccamo D, Campisi A, Curro M, Li Volti G, Vanella A, Ientile R. Excitotoxic and post-ischemic neurodegeneration: Involvement of transglutaminases. Amino Acids 2004; 27:373-9.
120. Hartman RE, Lee JM, Zipfel GJ, Wozniak DF. Characterizing learning deficits and hippocampal neuron loss following transient global cerebral ischemia in rats. Brain Res 2005; 1043:48-56.
121. Jaspers RM, Block F, Heim C, Sontag KH. Spatial learning is affected by transient occlusion of common carotid arteries (2VO): Comparison of behavioural and histopathological changes after '2VO' and 'four-vessel-occlusion' in rats. Neurosci Lett 1990; 117:149-53.
122. Yan B, Bi X, He J, Zhang Y, Thakur S, Xu H, et al. Quetiapine attenuates spatial memory impairment and hippocampal neurodegeneration induced by bilateral common carotid artery occlusion in mice. Life Sci 2007; 81:353-61.

123. Yan B, He J, Xu H, Zhang Y, Bi X, Thakur S, et al. Quetiapine attenuates the depressive and anxiolytic-like behavioural changes induced by global cerebral ischemia in mice. Behav Brain Res 2007; 182:36-41.
124. Yan B, Wang DY, Xing DM, Ding Y, Wang RF, Lei F, et al. The antidepressant effect of ethanol extract of radix puerariae in mice exposed to cerebral ischemia reperfusion. Pharmacol Biochem Behav 2004; 78:319-25.
125. Bryer JB, Starkstein SE, Votypka V, Parikh RM, Price TR, Robinson RG. Reduction of CSF monoamine metabolites in poststroke depression: A preliminary report. J Neuropsychiatry Clin Neurosci 1992; 4:440-2.
126. Mayberg HS, Parikh RM, Morris PL, Robinson RG. Spontaneous remission of post-stroke depression and temporal changes in cortical S2-serotonin receptors. J Neuropsychiatry Clin Neurosci 1991; 3:80-3.
127. Yuen EC, Mobley WC. Therapeutic potential of neurotrophic factors for neurological disorders. Ann Neurol 1996; 40:346-54.
128. Parikh V, Evans DR, Khan MM, Mahadik SP. Nerve growth factor levels in never medicated first episode psychotic patients and medicated chronic schizophrenic patients. Schizophr Res 2003; 60:117-23.
129. Fumagalli F, Molteni R, Bedogni, F, Gennarelli M, Perez J, Racagni G, et al. Quetiapine regulates FGF-2 and BDNF expression in the hippocampus of animals treated with MK-801. NeuroReport 2004; 15:2109-12.
130. Bruckheimer EM, Cho SH, Sarkiss M, Herrmann J, McDonnell TJ. The bcl-2 gene family and apoptosis. Adv Biochem Eng Biotechnol 1998; 62:75-105.
131. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 2005; 62:361-70.
132. Ming GL, Song H. Adult neurogenesis in the mammalian central nervous system. Annu Rev Neurosci 2005; 28:223-50.
133. Kodama M, Fujioka T, Duman RS. Chronic olanzapine or fluoxetine administration increases cell proliferation in hippocampus and prefrontal cortex of adult rat. Biol Psychiatry 2004; 56:570-80.
134. Wakade CG, Mahadik SP, Waller JL, Chiu FC. Atypical neuroleptics stimulate neurogenesis in adult rat brain. J Neurosci Res 2002; 69:72-9.
135. Roy NS, Wang S, Jiang L, Kang J, Benraiss A, Harrison-Restelli C, et al. In vitro neurogenesis by progenitor cells isolated from the adult human hippocampus. Nat Med 2000; 6:271-7.
136. Bruel-Jungerman E, Rampon C, Laroche S. Adult hippocampal neurogenesis, synaptic plasticity and memory: Facts and hypotheses. Rev Neurosci 2007; 18:93-114.
137. Newton SS, Duman RS. Neurogenic actions of atypical antipsychotic drugs and therapeutic implications. CNS Drugs 2007; 21:715-25.