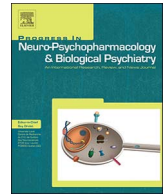




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The inhibition of the kynurenine pathway prevents behavioral disturbances and oxidative stress in the brain of adult rats subjected to an animal model of schizophrenia

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ABSTRACT

Evidence has shown that the kynurenine pathway (KP) plays a role in the onset of oxidative stress and also in the pathophysiology of schizophrenia. The aim of this study was to use a pharmacological animal model of schizophrenia induced by ketamine to investigate if KP inhibitors could protect the brains of Wistar rats against oxidative stress and behavioral changes. Ketamine, injected at the dose of 25 mg/kg, increased spontaneous locomotor activity. However, the inhibitors of tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenase (IDO) and kynurenine-3-monooxygenase (KMO) were able to reverse these changes. In addition, the IDO inhibitor prevented lipid peroxidation, and decreased the levels of protein carbonyl in the prefrontal cortex (PFC), hippocampus and striatum. It also increased the activity of superoxide dismutase (SOD) in the hippocampus, as well as increasing the levels of catalase activity in the PFC and hippocampus. The TDO inhibitor prevented lipid damage in the striatum and reduced the levels of protein carbonyl in the hippocampus and striatum. Also, the TDO inhibitor increased the levels of SOD activity in the striatum and CAT activity in the hippocampus of ketamine-induced pro-oxidant effects. Lipid damage was not reversed by the KMO inhibitor. The KMO inhibitor increased the levels of SOD activity in the hippocampus, and reduced the levels of protein carbonyl while elevating the levels of CAT activity in the striatum of rats that had been injected with ketamine. Our findings revealed that the KP pathway could be a potential mechanism by which a schizophrenia animal model induced by ketamine could cause interference by producing behavioral disturbance and inducing oxidative stress in the brain, suggesting that the inhibition of the KP pathway could be a potential target in treating schizophrenia.

1. Introduction

Schizophrenia is a severe, chronic and debilitating mental disorder

that affects 1% of the world's population. It is characterized by positive (hallucinations and paranoia), negative (blunted affect and social isolation) and cognitive symptoms (executive and memory dysfunction)

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(Larson et al. 2010). Data considers the disorder a result of a combination of genetic and environmental factors. Although its pathophysiology is not totally understood, biological studies support the involvement of several possible components including altered DNA methylation, and abnormal transmission of neurotransmitters, such as dopamine, glutamate, serotonin, and acetylcholine (Dauvermann et al., 2017; Maekawa et al., 2017; Tani et al., 2015; Wang et al., 2017). In addition, the pathophysiology of schizophrenia is explained by oxidative stress, nutritional deficiencies and infection (Maekawa et al., 2017; Réus et al., 2017).

Schizophrenic-like behavior can be induced by ketamine, an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor (Frohlich and Van Horn, 2014). Glutamatergic models of schizophrenia are used, since blocking of the NMDA receptor can reproduce specific aspects of this disorder. In fact, ketamine administration in rodents induces hyperlocomotion, a representative of the positive symptoms of schizophrenia (Canever et al., 2010; Ghedim et al., 2012; Réus et al., 2017). Additionally, in patients with schizophrenia, ketamine is found to exacerbate psychosis (Xu and Lipsky, 2015). The mechanism by which ketamine induces schizophrenia-like behavior and symptoms of psychosis is explained due to the hypofunction of the NMDA receptor (Roberts et al., 2010). Brain samples from patients with schizophrenia were found to have reduced levels of a protein which is associated with NMDA receptor function (Karlsgodt et al., 2011). Moreover, prenatal aberrations of the NMDA receptor might be associated with synaptic pruning in adolescence, and the onset of schizophrenia (Frohlich and Van Horn, 2014). It is postulated that hypofunction of the NMDA receptor induced by ketamine leads to increased levels of glutamate, which is mediated by gamma-aminobutyric acid (GABA) inhibitory interneurons, and these effects are implicated in the development of positive and negative symptoms (Nakazawa et al., 2012; Sone et al., 2007).

Evidence has shown a role for the kynurenine pathway (KP) in the pathophysiology of neuropsychiatric disorders, including depression and schizophrenia (Réus et al., 2015a; Würfel et al., 2017). Tryptophan (TRP) can be metabolized to serotonin or it can follow the kynurenine pathway via the action of tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO) into kynurenine (KYN) (Leklem, 1971; Cervenka et al., 2017). A polymorphism in the allele of IDO rs9657182 has been associated with schizophrenia (Golimbet et al., 2014). In addition, TDO2 mRNA expression was found to be increased in the prefrontal cortex of patients with schizophrenia (Miller et al., 2004). However, KYN is not neuroactive; when KYN is hydroxylated by kynurenine-3-monooxygenase (KMO) into 3-hydroxykynurenine (3-OHK), it can follow other pathways and be converted within microglial cells into one of the free radical generators, 3-hydroxykynurenine and 3-hydroxyanthranilic acid, as well as into quinolinic acid (QA), which is an agonist of the NMDA receptor (Guillemin et al., 2001). Also, KYN can be converted into kynurenic acid (KYNA) within astrocytes (Lopresti et al., 2014), with both QA and KYNA appearing to be neurotoxic. KYNA is an antagonist of the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) (Kessler et al., 1989; Blanco Ayala et al., 2015) and the NMDA receptor (Konradsson-Geuken et al., 2010). The effects of KYNA can induce hypnicotnergic and hypoglutamatergic conditions, and help to explain some aspects of the symptoms seen in schizophrenia (Koola et al., 2014; Lin et al., 2014). A meta-analysis review revealed that the levels of KYNA are elevated in patients with schizophrenia, mainly within the central nervous system (Plitman et al., 2017).

The balance of KP metabolites is essential in sustaining normal brain functions (Parasram, 2017). Indeed, metabolites of KP can become sources of oxidative stress, which is involved with the pathophysiology of schizophrenia (Fraguas et al., 2017; Onaolapo et al., 2017). Oxidative stress is a result of the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNA), and also a lower capacity within cellular antioxidant systems, which leads to damage to macromolecules such as protein and lipid (González Esquivel et al., 2017).

Patients with schizophrenia were found to have higher levels of malondialdehyde (MDA), a marker of lipid peroxidation, as well as reduced levels of antioxidants, including superoxide dismutase (SOD) (Gonzalez-Liencres et al., 2014). Animal models of schizophrenia induced by ketamine also demonstrated increases in the levels of MDA, and while zinc, a modulator of the NMDA receptor, reversed these changes (Onaolapo et al., 2017).

Based on the hypothesis that dysfunctions in the KP pathway and oxidative stress are involved in the pathophysiology of schizophrenia, we set out to investigate if inhibitors of the KP pathway (IDO, TDO and KMO) could prevent the ketamine-induced schizophrenia-like behavior and oxidative stress-induced damage seen in the brain areas involved with schizophrenia.

2. Material and methods

2.1. Animals

Adult male Wistar rats (250–300 g) were used in this study. All animals were housed under standard lighting conditions (12 h light/12 h dark with lights on between 6 a.m. and 6 p.m.). The adult male rats were housed two animals per cage, with food and water available ad libitum. The total number of rats for all experiments was 180. The experimental protocol was approved by the Animal Welfare Committee (AWC-14-0097) - Animal Research at UTHealth.

2.2. Experimental design and treatment

The animal model of schizophrenia was induced by administering ketamine at a dose of 25 mg/kg (ketamine HCL, Hospira, Inc., Illinois, USA). Ketamine was administered once a day, over 7 consecutive days via intraperitoneal (i.p.) injection, and was prepared in saline at a volume of 1 ml/100 g (Zugno et al., 2014, 2016). Inhibitors of the kynurenine pathway were used in animals that were subjected to an animal model of schizophrenia. The KP inhibitor, indoleamine 2,3-dioxygenase (IDO), 1-methyl-D-tryptophan (D-1MT, MW 218.25) was administered over a period of 7 days, and given at the same time as the ketamine. D-1MT was prepared in corn oil to produce a uniform volume of 10 ml/kg, and administered to the rats at dose of 500 mg/kg (3000 mg/m²) via gavage, using a ball-tipped needle (Jia et al., 2008). The animals were divided into four experimental groups ($n = 15$ per group): 1) control/vehicle; 2) control/(D-1MT); 3) ketamine/vehicle; 4) and ketamine/D-1MT. (Fig. 1A). The inhibitor of tryptofan indoleamine 2,3-dioxygenase (TDO), allopurinol (20 mg/kg, i.p.), was administered over a period of 7 days, and given at the same time as the ketamine (Gibney et al., 2014). The animals were divided into four experimental groups ($n = 15$ per group): 1) control/saline; 2) control/allopurinol; 3) ketamine/saline; and 4) ketamine/allopurinol (Fig. 1B). The inhibitor of kynurenine 3-monooxygenase (KMO), 3,4-dimethoxy-*N*-[4-(3-nitrophenylthiazol-2-yl)] benzenesulfonamide (Ro 61-8048) (100 mg/kg), or an equivalent volume of vehicle (0.1% Tween-80) (Urenjak and Obrenovitch, 2000) were given via the oral route. Ro 61-8048 was administered simultaneously with the first ketamine treatment, and then subsequently 48 and 96 h after the first administration. The animals were divided into four experimental groups ($n = 15$ per group): 1) control/vehicle; 2) control/Ro 61-8048; 3) ketamine/vehicle; and 4) ketamine/Ro 61-8048 (Fig. 1C).

2.3. Open-field test

The open-field task was used to evaluate locomotor activity, as described elsewhere in the literature (Zugno et al., 2014). For behavioral test was used a n of 15 rats per group. The distance travelled in an open arena was assessed for a period of 15 min. Locomotor activity was constantly monitored using an automated system installed in the arena.

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