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Linking phencyclidine intoxication to the tryptophan-kynurenine pathway: Therapeutic implications for schizophrenia

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ABSTRACT

Phencyclidine (PCP) is a dissociative anesthetic that induces psychotic symptoms and neurocognitive deficits in rodents similar to those observed in schizophrenia patients. PCP administration in healthy human subjects induces schizophrenia-like symptoms such as positive and negative symptoms, and a range of cognitive deficits. It has been reported that PCP, ketamine, and related drugs such as N-methyl-D-aspartate-type (NMDA) glutamate receptor antagonists, induce behavioral effects by blocking neurotransmission at NMDA receptors. Further, NMDA receptor antagonists reproduce specific aspects of the symptoms of schizophrenia. Neurochemical models based on the actions of PCP are well established, with increased focus on glutamatergic dysfunction as a basis for both symptoms and cognitive dysfunction in schizophrenia. On the other hand, the endogenous NMDA receptor antagonist, kynurenic acid (KYNA), which is a product of tryptophan-kynurenine pathway (KP) metabolism, is involved in schizophrenia pathogenesis. KYNA concentrations are elevated in the prefrontal cortex and cerebrospinal fluid of patients with schizophrenia. KYNA elevation affects neurotransmitter release in a similar manner to that of psychotomimetic agents such as PCP, underscoring a molecular basis of its involvement in schizophrenia pathophysiology. This review will highlight the relationship between PCP and KP metabolites based on evidence that both exogenous and endogenous NMDA receptor antagonists are involved in the pathogenesis of schizophrenia, and discuss our current understanding of the mechanisms underlying dysfunctional glutamatergic signaling as potential therapeutic targets for schizophrenia.

1. Introduction

The symptoms of schizophrenia are complex and are commonly divided into three different clusters (Andreasen, 1995). The positive symptoms of schizophrenia include hallucinations, delusions, bizarre behaviors, and perceptual distortions, whereas the negative symptoms are characterized by anhedonia and lack of interest. Schizophrenia patients have impairments in various cognitive functions, such as deficits in memory and attention, as well as lack of insight, judgment, and executive functions (Andreasen, 1995; Green et al., 2000).

Phencyclidine (PCP) was originally developed as a dissociative anesthetic in the 1950s. PCP was initially used as a surgical anesthetic, but due to its side effects (e.g., post-operative psychosis, severe anxiety, and dysphoria), its use in clinical studies was discontinued in 1965, and PCP

Abbreviations: PCP, phencyclidine; NMDA, N-methyl-D-aspartate; KYNA, kynurenic acid; KP, kynurenine pathway; CNS, central nervous system; QUIN, quinolinic acid; CaMKII, calmodulin kinase II; TRP, tryptophan; NAD^+, nicotinamide adenine dinucleotide; TDO, tryptophan 2,3-dioxygenase; IDO1,2, indoleamine 2,3-dioxygenase 1,2; KYN, kynurenine; IFN, interferon; LPS, lipopolysaccharide; KMO, kynurenine 3-monooxygenase; KAT, kynurenine aminotransferase; KYNU, kynureninase; 3-HK, 3-hydroxykynurenine; 3-HAA, 3-hydroxyanthranilic acid; XA, xanthrenic acid; 3-HAO, 3-hydroxyanthranilate 3,4-dioxygenase; QPRT, quinolinic acid phosphoribosyl transferase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; α7nAchR, α-7-nicotinic acetylcholine receptor

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was later utilized by veterinarians as an animal tranquilizer. PCP is addictive, and its use often leads to psychological dependence. Despite its adverse side effects, PCP became a popular drug of abuse known as "angel dust" in the 1970s. Although the demand for PCP decreased in the early 1990s, the estimated number of PCP-related emergency department visits increased by more than 400% between 2005 and 2011 (from 14,825 to 75,538 visits) in the USA (Bush, 2013). PCP induces a psychotomimetic state that closely resembles that of schizophrenia. Interestingly, PCP-induced psychosis incorporates both positive and negative symptoms as well as cognitive dysfunction resembling that of schizophrenia; thus, PCP has been widely used in animal models of schizophrenia (Javitt and Zukin, 1991; Mouri et al., 2007).

The etiology of schizophrenia has not been fully elucidated, but several theories have been proposed. The dopamine hypothesis of schizophrenia was first proposed in the 1960s. Patients with schizophrenia have increased dopaminergic activity that can be normalized with dopamine antagonists, particularly dopamine D2 receptor antagonists (Matthysse, 1974; Yang and Tsai, 2017). However, subsequent findings suggested that the dopamine hypothesis only partly explains the symptoms of schizophrenia, as dopamine receptor antagonists are not clinically effective for treating cortical-related symptoms of schizophrenia, such as negative symptoms and cognitive deficits (Yang and Tsai, 2017).

Over the past few decades, the glutamatergic hypofunction hypothesis has attracted interest in the field of schizophrenia research and has superseded the dopamine hypothesis. Glutamatergic models of schizophrenia were proposed based on the observation that PCP, ketamine, and related drugs induced schizophrenia-like psychotic effects (Javitt et al., 2012). These compounds induce schizophrenia-like symptoms by blocking neurotransmission at N-methyl-D-aspartate (NMDA) receptors. Since then, evidence supporting the role of NMDA receptor hypofunction in the pathophysiology of schizophrenia has accumulated. Compared to dopaminergic agents, NMDA receptor antagonists induce positive, negative, and cognitive symptoms of schizophrenia (Nabeshima et al., 2006). Further, clinical studies with PCP and ketamine have confirmed a close resemblance between NMDA receptor antagonist-induced symptoms and neurocognitive deficits and those observed in schizophrenia (Javitt et al., 2012). Furthermore, reduced glutamate levels in the cerebrospinal fluid of patients with schizophrenia supports this theory (Jayawickrama et al., 2015).

As a corollary of the glutamatergic hypofunction hypothesis, the kynurenic acid (KYNA) hypothesis has been recently proposed. KYNA is an endogenous NMDA receptor antagonist (Stone and Perkins, 1981). KYNA is a metabolite in the tryptophan-kynurenine pathway (KP). The roles of KP metabolites in central nervous system (CNS) diseases have garnered attention, as several KP metabolites, such as KYNA and quinolinic acid (QUIN), are neuroactive. Several publications have reported that KP metabolites in the brain are associated with various CNS diseases, including schizophrenia (Fujigaki et al., 2017; Lovelace et al., 2017; Stone and Darlington, 2013). Further, elevated KYNA concentrations are observed in the prefrontal cortex and cerebrospinal fluid of patients with schizophrenia (Erhardt et al., 2001; Schwarcz et al., 2001). Indeed, elevation of KYNA affects neurotransmitter release in a manner similar to that of psychotomimetic agents such as PCP, underscoring a molecular basis of its involvement in schizophrenia pathophysiology.

The purpose of this review is to (1) discuss the potential relationship between intoxication by PCP, KP metabolites, and NMDA receptors, (2) highlight how KP metabolites play a role in PCP intoxication, and (3) propose the manipulation of KP as a potential strategy for PCP-induced abnormal behavior, thereby serving as a potential therapeutic target for schizophrenia.

2. PCP intoxication

PCP is a water- or alcohol-soluble white crystalline powder that is often abused in powder, crystal, liquid, or tablet form. PCP exhibits dose-dependent effects that vary by administration route (within 2–5 min when smoked and within 30–60 min when taken orally). Intoxication lasts from 4 to 8 h, with some users experiencing effects for 24–48 h (Journey and Bentley, 2018). PCP abuse induces psychosis that is clinically indistinguishable from schizophrenia (Baldridge and Bessen, 1990; Rainey and Crowder, 1975). In a clinical study, acute PCP administration evoked transient schizophrenia-like symptoms, such as hyperactivity, paranoia, hallucinations, formal thought disorder, and cognitive impairments in normal volunteers, and exacerbated symptoms in schizophrenia patients (Javitt, 2007). Based on these clinical findings, the neurochemical effects of PCP have been investigated in animal models of schizophrenia (Moghaddam and Krystal, 2012; Mouri et al., 2007).

3. PCP and NMDA receptors

PCP-induced psychotomimetic effects are associated with submicromolar serum concentrations of PCP. At psychotomimetic concentrations in serum, PCP selectively binds to NMDA receptors as a noncompetitive antagonist (pKi: 6.18 ± 0.07) (Javitt and Zukin, 1991). Other NMDA receptor antagonists, such as the dissociative anesthetic ketamine and dizocilpine [(+) MK-801], also induce PCP-like psychotomimetic effects proportional to their potency in binding to NMDA receptors (Javitt and Zukin, 1991). The NMDA receptor is a ligand-gated Ca^{2+} channel. Ligand binding produces an influx of Ca^{2+} into the postsynaptic compartment (Nabeshima et al., 2006). Following NMDA receptor-mediated influx of Ca^{2+}, α-subunit Ca^{2+}/calmodulin kinase II (CaMKII) undergoes rapid phosphorylation at a threonine residue (Xia and Storm, 2005). It has been suggested that dysfunction in glutamatergic systems including NMDA-CaMKII signaling are involved in negative symptoms and cognitive deficits in PCP-treated mice, as well as in schizophrenia pathology (Nabeshima et al., 2006).

4. KP metabolites and NMDA receptors

4.1. Kynurenine pathway (KP)

As some of the metabolites of KP have neuroactive properties, there is accumulating evidence suggesting the dysregulation of KP is involved in the pathophysiology of several inflammation-related brain diseases such as depression, multiple sclerosis, and schizophrenia (Fujigaki et al., 2017; Majewski et al., 2016). An overview of the KP is presented in Fig. 1. The KP is the major route of tryptophan degradation in mammals. In most mammalian tissues, it is estimated that more than 95% of dietary TRP is metabolized via the KP, while the remaining TRP is metabolized by the serotonin and melatonin pathways (Stone and Darlington, 2002; Takikawa, 2005). The first and rate-limiting step in the KP is catalyzed by tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenase (IDO) 1 and 2 (Ball et al., 2007, 2009; Metz et al., 2007; Shimizu et al., 1978). These enzymes convert TRP to instable compound, N-formylkynurenine, which is then metabolized to L-kynurenine (KYN) by kynurenine formamidase. TDO is constitutively expressed in the liver and contributes to systemic levels of TRP and KYN (Miller et al., 2004). Unlike TDO, IDO1 and 2 are upregulated by proinflammatory cytokines and inflammatory stimuli such as interferon (IFN)-γ and lipopolysaccharide (LPS) (Connor et al., 2008; Fujigaki et al., 2006; Metz et al., 2007). Previous investigations have shown that the acceleration of KP metabolism by IDO1 has an important role in inflammation-mediated diseases and disorders (Saito et al., 1991, 1993).

KYN is then metabolized by at least three different enzymes: kynurenine 3-monooxygenase (KMO) (also referred to as kynurenine 3-hydoroxylase); kynurenine aminotransferase (KAT) 1, 2, 3, and 4; and kynureninase (KYNU) (Fujigaki et al., 2017; Schwarcz et al., 2012) (Fig. 1). Catabolism of KYN by KMO results in the production of 3-

Fig. 1. Tryptophan metabolism in kynurenine pathway. TRP, tryptophan; N′—F—KYN, N-formylkynurenine; KYN, kynurenine; KYNA, kynurenic acid; AA, anthranilic acid; 3-HK, 3-hydroxykynurenine; XA, xanthurenic acid; 3-HAA, 3-hydroxyanthranilic acid; ACMSD, 2-amino-3-carboxymuconic semialdehyde; QUIN, quinolinic acid; NAD+, nicotinamide adenine dinucleotide; IDO1,2, indoleamine 2,3-dioxygenase 1,2; TDO, tryptophan 2,3-dioxygenase; KYNF, kynurenine formamidase; KAT, kynurenine aminotransferase; KYNU, kynureninase; KMO, kynurenine 3-monooxygenase; 3-HAO, 3-hydroxyanthranilate 3,4-dioxygenase; QPRT, quinolinic acid phosphoribosyl transferase.

hydroxykynurenine (3-HK) and several downstream metabolites including the NMDA receptor agonist quinolinic acid (QUIN) (Fig. 1). Alternatively, KYN is metabolized to KYNA (which is considered a natural antagonist for the glycine-B co-agonist site of NMDA receptor) by KAT. Therefore, the KP is responsible for synthesizing both NMDA receptor agonist and antagonist.

4.2. KP metabolites and NMDA receptors

Over the past few decades, the roles of KP metabolites in the brain have been widely studied as they are implicated in various neurological diseases. Studies have reported that some KP metabolites are neurotoxic, whereas others have neuroprotective effects. Therefore, dysregulation of the KP may act as a double-edged sword. Here, we focus on two of the most widely studied metabolites: QUIN and KYNA, which are thought to have neurotoxic (NMDA receptor agonist) and neuroprotective (NMDA receptor antagonist) properties, respectively (Fig. 2).

4.2.1. QUIN and NMDA receptors

At CNS synapses, agonist binding to postsynaptic ionotropic glutamate receptors results in signaling between neurons. NMDA receptors comprise a unique receptor family that is activated in response to the concurrent binding of glutamate and glycine (Yu and Lau, 2018). An excessive amount of glutamate in the synaptic cleft results in dysregulation of Ca^{2+} homeostasis, mitochondrial dysfunction, and the generation of reactive oxygen species (Bohar et al., 2015). Under normal conditions, the amount of glutamate present is tightly regulated. In neurodegenerative diseases, this regulation is often disrupted, thus contributing to neuronal damage (Bohar et al., 2015). QUIN was identified as an endogenous selective agonist of NMDA receptors; QUIN

Fig. 2. The regulation of NMDA receptor by PCP, QUIN and KYNA. The potential sites of interaction of PCP, QUIN and KYNA for modulation of NMDA receptor function are shown. QUIN acts as a NMDA receptor agonist at glutamate binding site, whereas KYNA act as a NMDA receptor antagonist at glycine site. The endogenous QUIN and KYNA may interfere or amplify the PCP intoxication.

activates NMDA receptors, increases neuronal activity, and elevates intracellular Ca^{2+} concentrations (Stone and Perkins, 1981) (Fig. 2). Furthermore, QUIN causes selective neuronal lesions. Focal injections of QUIN into the striatum induces neurochemical, behavioral, and pathological changes (Schwarcz et al., 1983). A report by Beal et al. revealed that QUIN-induced striatal lesions more accurately replicated the histopathological features of Huntington's disease than did other known excitotoxins (Beal et al., 1986). QUIN also elicits cytotoxicity by increasing neuronal glutamate release, inhibiting astrocytic glutamate uptake, and inhibiting astroglial glutamine synthetase, leading to excessive microenvironmental glutamate concentrations and neurotoxicity (Baverel et al., 1990; Tavares et al., 2000, 2002).

4.2.2. KYNA and NMDA receptors

In contrast to QUIN, KYNA, a metabolite produced in the dead-end arm of the KP pathway (Fig. 1), has a neuroprotective role. KYNA acts as an antagonist of the NMDA receptor (Birch et al., 1988b; Kessler et al., 1989; Perkins and Stone, 1982; Reynolds et al., 1989) (Fig. 2). KYNA protects against neuronal damage caused by QUIN (NMDA receptor agonist); this effect is most likely mediated through the inhibitory activity of NMDA receptors (Stone, 1993). A body of evidence suggests that KYNA plays a protective role against excitotoxicity-induced neuronal death (Stone, 2000). KYNA acts as an inhibitor at the strychnine-insensitive glycine co-agonist site of NMDA receptors (Birch et al., 1988b). Further, KYNA also exerts weak antagonistic effects on kainate- and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-sensitive glutamate receptors (Birch et al., 1988a). KYNA has dual actions on AMPA receptors that manifest in a dose-dependent manner, evoking facilitation at low concentrations (nmol/L - μmol/L), and exerting neuroinhibition at higher concentrations (μmol/L - mmol/L) (Prescott et al., 2006; Szalardy et al., 2012). Another potential target may be the α-7-nicotinic acetylcholine receptor (α7nAchR), which KYNA has been reported to block (Hilmas et al., 2001). However, this result has not proved to be reproducible (Arnaiz-Cot et al., 2008; Dobelis et al., 2012; Mok et al., 2009), except that it is possibly present at high concentrations in young rats, and in a complex pharmacological mixture of receptor antagonists (Stone, 2007). Therefore, α7nAchR cannot currently be considered an established, proven target for KYNA.

KYNA is well established as an antagonist or inhibitor at several ionotropic receptors. However, it is still uncertain whether endogenous KYNA concentrations influence the activity of these receptors. An argument against the physiological relevance of this activity is that inhibition is only observed at concentrations that are substantially higher than those typically found endogenously in the CNS. For example,

although basal extracellular concentrations of KYNA in the rat brain fall within the low nmol/L range (10–20 nmol/L), KYNA can act as a non-competitive antagonist at the glycine binding site on the NR1 subunit of the NMDA receptor, at high concentrations (10–20 μmol/L) under physiological conditions (Stone, 1993). In addition, higher concentrations (200–500 μmol/L) of KYNA are required to exert inhibitory effects on NMDA receptor function upon binding to the glutamate recognition site (Kessler et al., 1989). Furthermore, the affinity of KYNA for NMDA receptors is weaker than those of other NMDA receptor antagonists. For example, the Ki value of KYNA was 7.33 μmol/L for the [^{3}H]glycine binding to hippocampal membranes (Berger, 1995), whereas the Ki of PCP was 7.12 nmol/L for the PCP-binding site (Roth et al., 2013). KYNA also exerts inhibitory actions on AMPA receptors; however, the required concentrations are even higher, falling within the range of high μmol/L to mmol/L (Swartz et al., 1990). Nevertheless, it is possible that the KYNA concentration in the blood or CSF does not reflect the higher concentrations of KYNA in the immediate surroundings of the cells from which they are generated and released. Hence, further studies are required to elucidate the actions of KYNA on these receptors under physiological conditions (see (Szalardy et al., 2012), for review).

5. PCP and KYNA intoxication in the context of schizophrenia

Both exogenous PCP and endogenous KYNA are related to schizophrenia-like behavioral changes in rodents and symptoms of schizophrenia patients.

5.1. Behavioral abnormalities induced by PCP administration

As mentioned in section 2, acute PCP administration evoked transient schizophrenia-like symptoms, such as hyperactivity, paranoia, hallucinations, formal thought disorder, and cognitive impairments in normal volunteers, and exacerbated symptoms in schizophrenia patients (Javitt, 2007). Thus, PCP has been widely used for modeling schizophrenia in animals (Gilmour et al., 2012; Mouri et al., 2007). Acute and repeated PCP administration in mice impaired attention and latent learning in a water finding test (Noda et al., 2001), and this impairment was reversed by acute treatment with clozapine, but not with haloperidol. Since the effects of atypical antipsychotics are consistent with the clinical effects, administration of PCP in rodents are believed to be useful as a behavioral model of cognitive deficits of schizophrenia (Mouri et al., 2007; Nabeshima et al., 2006; Noda et al., 2001). Further, PCP administration in rodents could mimics several psychotic symptoms in schizophrenia patients, such as hyperlocomotion (Johnson et al., 1998; Mouri et al., 2012; Noda et al., 1995; Sturgeon et al., 1979), object recognition memory impairment (Hida et al., 2015; Mouri et al., 2012; Tanaka et al., 2011), and reduced social behavior (Qiao et al., 2001; Sams-Dodd, 1995; Wang et al., 2007) (for a review, see (Jones et al., 2011)).

5.2. Behavioral abnormalities induced by elevated endogenous KYNA

As is the case with administration of PCP, elevated levels of endogenous KYNA are related to behavioral abnormalities. In an animal model using rats, elevation of endogenous KYNA levels produced deficits in spatial and working memory consistent with symptom etiology in schizophrenia (Chess et al., 2007). Administration of KYN, the precursor of KYNA, produced clinically relevant increases in KYNA concentration in the rat brain and impaired contextual fear memory (Chess et al., 2009). Further, elevation of endogenous KYNA by administration of KYN significantly disrupted PPI, a model that reflects sensory gating deficits in schizophrenia patients (Erhardt et al., 2004). Furthermore, gene deficiency in KMO, which is located at the branch point of KP (Fig. 1), shunts the pathway towards the synthesis of KYNA, resulting in significantly increased KYNA levels in the brain and periphery (Erhardt et al., 2017; Tashiro et al., 2017). We have reported that KMO knockout mice show depressive-like behaviors, such as decreased sucrose preference and increased immobility in the forced swimming test, and high anxiety as shown by decreased time spent in the center area of the open field test (Tashiro et al., 2017). Using the same mouse strain, another group also reported behavioral abnormalities such as impairments in contextual memory, social interaction, and increased anxiety-like behavior (Erhardt et al., 2017).

6. Possible therapeutic approach for PCP psychosis through the KP

As previously mentioned, the KP leads to the production of agonists (QUIN) and antagonists (KYNA) of NMDA receptors. Although little is known about the relationship between PCP intoxication and endogenous KP metabolites, there are several reports which led us to speculate a possible therapeutic approach for PCP intoxication through manipulation of the KP (Fig. 2).

Tuboly et al. suggested that the effects of KYNA on ionotropic glutamate receptors at the spinal level are primarily due to the inhibition of NMDA receptors at both glycine and PCP binding sites (Tuboly et al., 2015). Another report using NMDA receptor antagonists such as ketamine, have demonstrated that a brain-penetrable inhibitor of KAT2, which may be responsible for the majority of brain KYNA synthesis (Nematollahi et al., 2016; Schwarcz et al., 2012), dose-dependently reduced brain KYNA, prevented amphetamine and ketamine-induced disruption of auditory gating, and improved performance in a sustained attention task. It also prevented ketamine-induced disruption of performance in a working and spatial memory tasks in rodents and non-human primates, respectively (Kozak et al., 2014).

In contrast, elevation of endogenous QUIN may counteract PCP-induced behavioral abnormalities. Since QUIN is a selective NMDA receptor agonist, elevation of endogenous QUIN could neutralize PCP intoxication. Indeed, pretreatment with D-serine (an endogenous NMDA receptor agonist) or SSR504734 (a potent glycine transporter type 1 inhibitor which potentiates NMDA receptor function by increasing synaptic levels of glycine), completely inhibited functional magnetic resonance imaging responses to PCP (Gozzi et al., 2008). Manipulating QUIN levels may improve PCP intoxication; however, caution must be exercised since QUIN has excitatory effects on neurons.

7. Conclusion

Recent studies have proposed that several factors such as serotonin, acetylcholine, gamma-aminobutyric acid, and inflammation, are associated with the pathogenesis of schizophrenia. However, the mechanisms of schizophrenia pathogenesis are still unclear. PCP-related animal models are a useful tool for understanding the pathophysiology of schizophrenia. Since both exogenous and endogenous NMDA receptor antagonists such as PCP and KYNA, respectively, have several common effects, we believe that understanding the mechanisms underpinning dysfunction of glutamatergic systems will contribute to therapeutic developments for schizophrenia.

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Appendix A. Supplementary data

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References

Andreasen, N.C., 1995. Symptoms, signs, and diagnosis of schizophrenia. Lancet 346, 477–481.

Arnaiz-Cot, J.J., Gonzalez, J.C., Sobrado, M., Baldelli, P., Carbone, E., Gandia, L., Garcia, A.G., Hernandez-Guijo, J.M., 2008. Allosteric modulation of alpha 7 nicotinic receptors selectively depolarizes hippocampal interneurons, enhancing spontaneous gabaergic transmission. Eur. J. Neurosci. 27, 1097–1110.

Baldridge, E.B., Bessen, H.A., 1990. Phencyclidine. Emerg. Med. Clin. N. Am. 8, 541–550.

Ball, H.J., Sanchez-Perez, A., Weiser, S., Austin, C.J., Astelbauer, F., Miu, J., McQuillan, J.A., Stocker, R., Jermiin, L.S., Hunt, N.H., 2007. Characterization of an indoleamine 2,3-dioxygenase-like protein found in humans and mice. Gene 396, 203–213.

Ball, H.J., Yuasa, H.J., Austin, C.J., Weiser, S., Hunt, N.H., 2009. Indoleamine 2,3-dioxygenase-2; a new enzyme in the kynurenine pathway. Int. J. Biochem. Cell Biol. 41, 467–471.

Baverel, G., Martin, G., Michoudet, C., 1990. Glutamine synthesis from aspartate in Guinea-pig renal cortex. Biochem. J. 268, 437–442.

Beal, M.F., Kowall, N.W., Ellison, D.W., Mazurek, M.F., Swartz, K.J., Martin, J.B., 1986. Replication of the neurochemical characteristics of huntington's disease by quinolinic acid. Nature 321, 168–171.

Berger, M.L., 1995. On the true affinity of glycine for its binding site at the nmda receptor complex. J. Pharmacol. Toxicol. Methods 34, 79–88.

Birch, P.J., Grossman, C.J., Hayes, A.G., 1988a. Kynurenate and fg9041 have both competitive and non-competitive antagonist actions at excitatory amino acid receptors. Eur. J. Pharmacol. 151, 313–315.

Birch, P.J., Grossman, C.J., Hayes, A.G., 1988b. Kynurenic acid antagonises responses to nmda via an action at the strychnine-insensitive glycine receptor. Eur. J. Pharmacol. 154, 85–87.

Bohar, Z., Toldi, J., Fulop, F., Vecsei, L., 2015. Changing the face of kynurenines and neurotoxicity: therapeutic considerations. Int. J. Mol. Sci. 16, 9772–9793.

Bush, D.M., 2013. Emergency Department Visits Involving Phencyclidine (Pcp). The cbhsq report, Rockville (MD). pp. 1–8.

Chess, A.C., Landers, A.M., Bucci, D.J., 2009. L-kynurenine treatment alters contextual fear conditioning and context discrimination but not cue-specific fear conditioning. Behav. Brain Res. 201, 325–331.

Chess, A.C., Simoni, M.K., Alling, T.E., Bucci, D.J., 2007. Elevations of endogenous kynurenic acid produce spatial working memory deficits. Schizophr. Bull. 33, 797–804.

Connor, T.J., Starr, N., O'Sullivan, J.B., Harkin, A., 2008. Induction of indolamine 2,3-dioxygenase and kynurenine 3-monooxygenase in rat brain following a systemic inflammatory challenge: a role for ifn-gamma? Neurosci. Lett. 441, 29–34.

Dobelis, P., Staley, K.J., Cooper, D.C., 2012. Lack of modulation of nicotinic acetylcholine alpha-7 receptor currents by kynurenic acid in adult hippocampal interneurons. PLoS One 7, e41108.

Erhardt, S., Blennow, K., Nordin, C., Skogh, E., Lindstrom, L.H., Engberg, G., 2001. Kynurenic acid levels are elevated in the cerebrospinal fluid of patients with schizophrenia. Neurosci. Lett. 313, 96–98.

Erhardt, S., Pocivavsek, A., Repici, M., Liu, X.C., Imbeault, S., Maddison, D.C., Thomas, M.A.R., Smalley, J.L., Larsson, M.K., Muchowski, P.J., Giorgini, F., Schwarcz, R., 2017. Adaptive and behavioral changes in kynurenine 3-monooxygenase knockout mice: relevance to psychotic disorders. Biol. Psychiatry 82, 756–765.

Erhardt, S., Schwieler, L., Emanuelsson, C., Geyer, M., 2004. Endogenous kynurenic acid disrupts prepulse inhibition. Biol. Psychiatry 56, 255–260.

Fujigaki, H., Saito, K., Fujigaki, S., Takemura, M., Sudo, K., Ishiguro, H., Seishima, M., 2006. The signal transducer and activator of transcription 1alpha and interferon regulatory factor 1 are not essential for the induction of indoleamine 2,3-dioxygenase by lipopolysaccharide: involvement of p38 mitogen-activated protein kinase and nuclear factor-kappab pathways, and synergistic effect of several proinflammatory cytokines. J. Biochem. 139, 655–662.

Fujigaki, H., Yamamoto, Y., Saito, K., 2017. L-tryptophan-kynurenine pathway enzymes are therapeutic target for neuropsychiatric diseases: focus on cell type differences. Neuropharmacology 112, 264–274.

Gilmour, G., Dix, S., Fellini, L., Gastambide, F., Plath, N., Steckler, T., Talpos, J., Tricklebank, M., 2012. Nmda receptors, cognition and schizophrenia–testing the validity of the nmda receptor hypofunction hypothesis. Neuropharmacology 62, 1401–1412.

Gozzi, A., Herdon, H., Schwarz, A., Bertani, S., Crestan, V., Turrini, G., Bifone, A., 2008. Pharmacological stimulation of nmda receptors via co-agonist site suppresses fmri response to phencyclidine in the rat. Psychopharmacology (Berlin) 201, 273–284.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr. Bull. 26, 119–136.

Hida, H., Mouri, A., Mori, K., Matsumoto, Y., Seki, T., Taniguchi, M., Yamada, K., Iwamoto, K., Ozaki, N., Nabeshima, T., Noda, Y., 2015. Blonanserin ameliorates phencyclidine-induced visual-recognition memory deficits: the complex mechanism of blonanserin action involving d(3)-5-ht(2)a and d(1)-nmda receptors in the mpfc. Neuropsychopharmacology 40, 601–613.

Hilmas, C., Pereira, E.F., Alkondon, M., Rassoulpour, A., Schwarcz, R., Albuquerque, E.X., 2001. The brain metabolite kynurenic acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications. J. Neurosci. 21, 7463–7473.

Javitt, D.C., 2007. Glutamate and schizophrenia: phencyclidine, n-methyl-d-aspartate receptors, and dopamine-glutamate interactions. Int. Rev. Neurobiol. 78, 69–108.

Javitt, D.C., Zukin, S.R., 1991. Recent advances in the phencyclidine model of schizophrenia. Am. J. Psychiatry 148, 1301–1308.

Javitt, D.C., Zukin, S.R., Heresco-Levy, U., Umbricht, D., 2012. Has an angel shown the way? Etiological and therapeutic implications of the pcp/nmda model of schizophrenia. Schizophr. Bull. 38, 958–966.

Jayawickrama, G.S., Sadig, R.R., Sun, G., Nematollahi, A., Nadvi, N.A., Hanrahan, J.R., Gorrell, M.D., Church, W.B., 2015. Kynurenine aminotransferases and the prospects of inhibitors for the treatment of schizophrenia. Curr. Med. Chem. 22, 2902–2918.

Johnson, K.M., Phillips, M., Wang, C., Kevetter, G.A., 1998. Chronic phencyclidine induces behavioral sensitization and apoptotic cell death in the olfactory and piriform cortex. J. Neurosci. Res. 52, 709–722.

Jones, C.A., Watson, D.J., Fone, K.C., 2011. Animal models of schizophrenia. Br. J. Pharmacol. 164, 1162–1194.

Journey, J.D., Bentley, T.P., 2018. Phencyclidine (Pcp) Toxicity, Statpearls, Treasure Island (FL).

Kessler, M., Terramani, T., Lynch, G., Baudry, M., 1989. A glycine site associated with n-methyl-d-aspartic acid receptors: characterization and identification of a new class of antagonists. J. Neurochem. 52, 1319–1328.

Kozak, R., Campbell, B.M., Strick, C.A., Horner, W., Hoffmann, W.E., Kiss, T., Chapin, D.S., McGinnis, D., Abbott, A.L., Roberts, B.M., Fonseca, K., Guanowsky, V., Young, D.A., Seymour, P.A., Dounay, A., Hajos, M., Williams, G.V., Castner, S.A., 2014. Reduction of brain kynurenic acid improves cognitive function. J. Neurosci. 34, 10592–10602.

Lovelace, M.D., Varney, B., Sundaram, G., Lennon, M.J., Lim, C.K., Jacobs, K., Guillemin, G.J., Brew, B.J., 2017. Recent evidence for an expanded role of the kynurenine pathway of tryptophan metabolism in neurological diseases. Neuropharmacology 112, 373–388.

Majewski, M., Kozlowska, A., Thoene, M., Lepiarczyk, E., Grzegorzewski, W.J., 2016. Overview of the role of vitamins and minerals on the kynurenine pathway in health and disease. J. Physiol. Pharmacol. 67, 3–19.

Matthysse, S., 1974. Dopamine and the pharmacology of schizophrenia: the state of the evidence. J. Psychiatr. Res. 11, 107–113.

Metz, R., Duhadaway, J.B., Kamasani, U., Laury-Kleintop, L., Muller, A.J., Prendergast, G.C., 2007. Novel tryptophan catabolic enzyme Ido2 is the preferred biochemical target of the antitumor indoleamine 2,3-dioxygenase inhibitory compound d-1-methyl-tryptophan. Cancer Res. 67, 7082–7087.

Miller, C.L., Llenos, I.C., Dulay, J.R., Barillo, M.M., Yolken, R.H., Weis, S., 2004. Expression of the kynurenine pathway enzyme tryptophan 2,3-dioxygenase is increased in the frontal cortex of individuals with schizophrenia. Neurobiol. Dis. 15, 618–629.

Moghaddam, B., Krystal, J.H., 2012. Capturing the angel in "angel dust": twenty years of translational neuroscience studies of nmda receptor antagonists in animals and humans. Schizophr. Bull. 38, 942–949.

Mok, M.H., Fricker, A.C., Weil, A., Kew, J.N., 2009. Electrophysiological characterisation of the actions of kynurenic acid at ligand-gated ion channels. Neuropharmacology 57, 242–249.

Mouri, A., Koseki, T., Narusawa, S., Niwa, M., Mamiya, T., Kano, S., Sawa, A., Nabeshima, T., 2012. Mouse strain differences in phencyclidine-induced behavioural changes. Int. J. Neuropsychopharmacol. 15, 767–779.

Mouri, A., Noda, Y., Enomoto, T., Nabeshima, T., 2007. Phencyclidine animal models of schizophrenia: approaches from abnormality of glutamatergic neurotransmission and neurodevelopment. Neurochem. Int. 51, 173–184.

Nabeshima, T., Mouri, A., Murai, R., Noda, Y., 2006. Animal model of schizophrenia: dysfunction of nmda receptor-signaling in mice following withdrawal from repeated administration of phencyclidine. Ann. N. Y. Acad. Sci. 1086, 160–168.

Nematollahi, A., Sun, G., Jayawickrama, G.S., Church, W.B., 2016. Kynurenine aminotransferase isozyme inhibitors: a review. Int. J. Mol. Sci. 17.

Noda, A., Noda, Y., Kamei, H., Ichihara, K., Mamiya, T., Nagai, T., Sugiura, S., Furukawa, H., Nabeshima, T., 2001. Phencyclidine impairs latent learning in mice: interaction between glutamatergic systems and sigma(1) receptors. Neuropsychopharmacology 24, 451–460.

Noda, Y., Yamada, K., Furukawa, H., Nabeshima, T., 1995. Enhancement of immobility in a forced swimming test by subacute or repeated treatment with phencyclidine: a new model of schizophrenia. Br. J. Pharmacol. 116, 2531–2537.

Perkins, M.N., Stone, T.W., 1982. An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid. Brain Res. 247, 184–187.

Prescott, C., Weeks, A.M., Staley, K.J., Partin, K.M., 2006. Kynurenic acid has a dual action on ampa receptor responses. Neurosci. Lett. 402, 108–112.

Qiao, H., Noda, Y., Kamei, H., Nagai, T., Furukawa, H., Miura, H., Kayukawa, Y., Ohta, T., Nabeshima, T., 2001. Clozapine, but not haloperidol, reverses social behavior deficit in mice during withdrawal from chronic phencyclidine treatment. Neuroreport 12, 11–15.

Rainey Jr., J.M., Crowder, M.K., 1975. Prolonged psychosis attributed to phencyclidine: report of three cases. Am. J. Psychiatry 132, 1076–1078.

Reynolds, I.J., Harris, K.M., Miller, R.J., 1989. Nmda receptor antagonists that bind to the strychnine-insensitive glycine site and inhibit nmda-induced ca2+ fluxes and [3h] gaba release. Eur. J. Pharmacol. 172, 9–17.

Roth, B.L., Gibbons, S., Arunotayanun, W., Huang, X.P., Setola, V., Treble, R., Iversen, L., 2013. The ketamine analogue methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate nmda receptor. PLoS One 8, e59334.

Saito, K., Markey, S.P., Heyes, M.P., 1991. Chronic effects of gamma-interferon on quinolinic acid and indoleamine-2,3-dioxygenase in brain of c57bl6 mice. Brain Res. 546, 151–154.

Saito, K., Nowak Jr., T.S., Suyama, K., Quearry, B.J., Saito, M., Crowley, J.S., Markey, S.P., Heyes, M.P., 1993. Kynurenine pathway enzymes in brain: responses to ischemic brain injury versus systemic immune activation. J. Neurochem. 61, 2061–2070.

Sams-Dodd, F., 1995. Automation of the social interaction test by a video-tracking system:

behavioural effects of repeated phencyclidine treatment. J. Neurosci. Methods 59, 157–167.
Schwarcz, R., Bruno, J.P., Muchowski, P.J., Wu, H.Q., 2012. Kynurenines in the mammalian brain: when physiology meets pathology. Nat. Rev. Neurosci. 13, 465–477.
Schwarcz, R., Rassoulpour, A., Wu, H.Q., Medoff, D., Tamminga, C.A., Roberts, R.C., 2001. Increased cortical kynurenate content in schizophrenia. Biol. Psychiatry 50, 521–530.
Schwarcz, R., Whetsell Jr., W.O., Mangano, R.M., 1983. Quinolinic acid: an endogenous metabolite that produces axon-sparing lesions in rat brain. Science 219, 316–318.
Shimizu, T., Nomiyama, S., Hirata, F., Hayaishi, O., 1978. Indoleamine 2,3-dioxygenase. Purification and some properties. J. Biol. Chem. 253, 4700–4706.
Stone, T.W., 1993. Neuropharmacology of quinolinic and kynurenic acids. Pharmacol. Rev. 45, 309–379.
Stone, T.W., 2000. Development and therapeutic potential of kynurenic acid and kynurenine derivatives for neuroprotection. Trends Pharmacol. Sci. 21, 149–154.
Stone, T.W., 2007. Kynurenic acid blocks nicotinic synaptic transmission to hippocampal interneurons in young rats. Eur. J. Neurosci. 25, 2656–2665.
Stone, T.W., Darlington, L.G., 2002. Endogenous kynurenines as targets for drug discovery and development. Nat. Rev. Drug Discov. 1, 609–620.
Stone, T.W., Darlington, L.G., 2013. The kynurenine pathway as a therapeutic target in cognitive and neurodegenerative disorders. Br. J. Pharmacol. 169, 1211–1227.
Stone, T.W., Perkins, M.N., 1981. Quinolinic acid: a potent endogenous excitant at amino acid receptors in cns. Eur. J. Pharmacol. 72, 411–412.
Sturgeon, R.D., Fessler, R.G., Meltzer, H.Y., 1979. Behavioral rating scales for assessing phencyclidine-induced locomotor activity, stereotyped behavior and ataxia in rats. Eur. J. Pharmacol. 59, 169–179.
Swartz, K.J., During, M.J., Freese, A., Beal, M.F., 1990. Cerebral synthesis and release of kynurenic acid: an endogenous antagonist of excitatory amino acid receptors. J. Neurosci. 10, 2965–2973.
Szalardy, L., Zadori, D., Toldi, J., Fulop, F., Klivenyi, P., Vecsei, L., 2012. Manipulating kynurenic acid levels in the brain - on the edge between neuroprotection and cognitive dysfunction. Curr. Top. Med. Chem. 12, 1797–1806.
Takikawa, O., 2005. Biochemical and medical aspects of the indoleamine 2,3-dioxygenase-initiated l-tryptophan metabolism. Biochem. Biophys. Res. Commun. 338, 12–19.
Tanaka, D.H., Toriumi, K., Kubo, K., Nabeshima, T., Nakajima, K., 2011. Gabaergic precursor transplantation into the prefrontal cortex prevents phencyclidine-induced cognitive deficits. J. Neurosci. 31, 14116–14125.
Tashiro, T., Murakami, Y., Mouri, A., Imamura, Y., Nabeshima, T., Yamamoto, Y., Saito, K., 2017. Kynurenine 3-monooxygenase is implicated in antidepressants-responsive depressive-like behaviors and monoaminergic dysfunctions. Behav. Brain Res. 317, 279–285.
Tavares, R.G., Tasca, C.I., Santos, C.E., Alves, L.B., Porciuncula, L.O., Emanuelli, T., Souza, D.O., 2002. Quinolinic acid stimulates synaptosomal glutamate release and inhibits glutamate uptake into astrocytes. Neurochem. Int. 40, 621–627.
Tavares, R.G., Tasca, C.I., Santos, C.E., Wajner, M., Souza, D.O., Dutra-Filho, C.S., 2000. Quinolinic acid inhibits glutamate uptake into synaptic vesicles from rat brain. Neuroreport 11, 249–253.
Tuboly, G., Tar, L., Bohar, Z., Safrany-Fark, A., Petrovszki, Z., Kekesi, G., Vecsei, L., Pardutz, A., Horvath, G., 2015. The inimitable kynurenic acid: the roles of different ionotropic receptors in the action of kynurenic acid at a spinal level. Brain Res. Bull. 112, 52–60.
Wang, D., Noda, Y., Zhou, Y., Nitta, A., Furukawa, H., Nabeshima, T., 2007. Synergistic effect of galantamine with risperidone on impairment of social interaction in phencyclidine-treated mice as a schizophrenic animal model. Neuropharmacology 52, 1179–1187.
Xia, Z., Storm, D.R., 2005. The role of calmodulin as a signal integrator for synaptic plasticity. Nat. Rev. Neurosci. 6, 267–276.
Yang, A.C., Tsai, S.J., 2017. New targets for schizophrenia treatment beyond the dopamine hypothesis. Int. J. Mol. Sci. 18.
Yu, A., Lau, A.Y., 2018. Glutamate and glycine binding to the nmda receptor. Structure 26, 1035–1043 e1032.