Neuropharmacology 112 (2017) 297–306

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

The kynurenine pathway in schizophrenia and bipolar disorder

Sophie Erhardt*, Lilly Schwieler, Sophie Imbeault, Göran Engberg

Department of Physiology and Pharmacology, Karolinska Institutet, SE-171 77, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 29 December 2015
Received in revised form
26 May 2016
Accepted 27 May 2016
Available online 28 May 2016

Keywords:
Kynurenic acid
Psychosis
Bipolar disorder
Cytokines
KMO
KAT II
IL-1b

ABSTRACT

The kynurenine pathway of tryptophan degradation generates several neuroactive compounds. Of those, kynurenic acid is an *N*-methyl-D-aspartate (NMDA) and alpha7 nicotinic receptor antagonist. The kynurenic acid hypothesis of schizophrenia is built upon the fact that kynurenic acid blocks glutamate receptors and is elevated in schizophrenia. Kynurenic acid tightly controls glutamatergic and dopaminergic neurotransmission and elevated brain levels appear related to psychotic symptoms and cognitive impairments. Contributing to enhanced production of kynurenic acid, the expression and enzyme activity of kynurenine 3-monooxygenase (KMO) are reduced in schizophrenia and in bipolar patients with a history of psychosis. The kynurenine pathway is also critically regulated by cytokines, and, indeed, the pro-inflammatory cytokines interleukin (IL)-1β and IL-6 are elevated in schizophrenia and bipolar disorder and stimulate the production of kynurenic acid. One physiological mechanism controlling the activity of the kynurenine pathway originates from the protein sorting nexin 7 (SNX7). This glial signaling pathway initiates a caspase-8-driven activation of IL-1β that induces tryptophan-2,3-dioxygenase 2 (TDO2), an enzyme in the kynurenine pathway. A recent study shows that a genetic variation resulting in decreased expression of SNX7 is linked to increased central levels of kynurenic acid and ultimately to psychosis and cognitive dysfunction in bipolar disorder. Experimental studies highlight the detrimental effects of increased synthesis of kynurenic acid during sensitive periods of early brain development. Furthermore, experimental studies strongly support inhibition of kynurenine aminotransferase (KAT) II as a novel target and a valuable pharmacological strategy in the treatment of psychosis and for improving cognitive performance relevant for schizophrenia.

This article is part of the Special Issue entitled 'The Kynurenine Pathway in Health and Disease'.

Contents

1. Introduction

Schizophrenia and bipolar disorder are two severe psychiatric

* Corresponding author.
E-mail address: sophie.erhardt@ki.se (S. Erhardt).

http://dx.doi.org/10.1016/j.neuropharm.2016.05.020
0028-3908/

disorders and the burden of these illnesses is overwhelming in terms of disability, impaired psychosocial functioning and premature death (Murray and Lopez, 1996). Both disorders typically strike maturing individuals just when they are entering into adulthood and the total expenses for society, including direct costs for health care and indirect costs for production losses, for individuals with schizophrenia or bipolar disorders is enormous (Gustavsson et al., 2011; Ekman et al., 2013a, 2013b).

The symptoms and signs of schizophrenia are complex and diverse, and commonly divided into three different clusters (see Andreasen et al., 1996). The positive symptoms of schizophrenia include hallucinations (usually in the form of voices, and often exhortatory in their message), delusions (often paranoid in nature), bizarre behavior and perceptual distortions, whereas the negative symptoms are characterized by a decrease or loss of normal functions. These symptoms include alogia, avolition, apathy, anhedonia as well as blunting of emotions and withdrawal from social contacts. Patients with schizophrenia also have impairment in various cognitive functions, such as deficits in memory and attention as well as lack of insight, judgment, and executive functions (see Green et al., 2000).

Although antipsychotics have shown therapeutic effects for positive symptoms such as delusions and hallucinations, other domains of schizophrenic symptoms e.g. negative symptoms and cognitive disturbances only show marginal response to antipsychotic therapy (Green, 1996). Present therapy, with the roots in the late 1950s, is unfavorable, and novel treatment is urgently needed. However, our lack of insight into the pathophysiological mechanisms has hampered treatment strategies directed towards causative targets.

Schizophrenia and bipolar disorders share many characteristics and symptoms overlap. Delusions and/or hallucinations are hallmarks of schizophrenia but a substantial part of bipolar disorder patients also experience similar but less pronounced symptoms during episodes of abnormal mood (Dunayevich and Keck, 2000). For instance, acute mania including psychotic features in bipolar disorder type I can be difficult to distinguish from an acute psychosis in schizophrenia. In similarity to schizophrenia, the manic and psychotic symptoms seen in bipolar disorder are believed to stem from hyperactivity in limbic areas and respond to dopamine blockade with existing antipsychotics. As in schizophrenia, core features of bipolar disorders are also specific cognitive deficits in verbal learning and memory as well as in attention and executive function (Yatham et al., 2010).

Both schizophrenia and bipolar disorder are highly heritable (60–80%; Kieseppa et al., 2004; Lichtenstein et al., 2009; Sullivan et al., 2003) and family and twin studies have revealed a partial overlap in genetic susceptibility of the two disorders. An extensive molecular genetic study, has suggested a genetic correlation of 68%, calculated using common single nucleotide polymorphisms (SNPs), and further implied a polygenic basis for both disorders (Cross-Disorder Group of the Psychiatric Genomics et al., 2013). Several chromosomal regions, including 10p14, 18p11, 13q32, 8p22 and 22q11 (Berrettini, 2003; Bramon and Sham, 2001), as well as a number of genes, including G72, BDNF and COMT (Chumakov et al., 2002; Hattori et al., 2003; Kirov et al., 1998; Kunugi et al., 1997; Neves-Pereira et al., 2002; Rosa et al., 2006; Schumacher et al., 2004; Shifman et al., 2002), have been linked to increased risk for bipolar disorder and schizophrenia.

In the absence of disease biomarkers, diagnoses of schizophrenia and bipolar disorder are based on clinical phenomenology only. Clearly, this hampers patient stratification as well as detection of patients early in the disease phase. Understanding pathophysiological mechanisms behind symptoms and the increased risk for suicide that accompany these disorders remain the most fascinating yet challenging questions in neurobiology and is a prerequisite for the development of improved diagnostic tools, treatment strategies, and rational drug design.

2. The kynurenic acid hypothesis of schizophrenia

The dopamine hypothesis has for decades dominated theories regarding the pathophysiology of schizophrenia, and it is generally believed that many symptoms associated with the disease are mediated via the mesolimbic and mesocortical dopamine systems. In the past decades though, it has become clear that dopamine is just part of the story and that the main abnormalities lie elsewhere (Grace, 1991). In this regard the model of glutamatergic dysfunction has attracted growing interest and the origin of this theory lies in the discovery that *N*-methyl-D-aspartate (NMDA) receptor antagonists, like phencyclidine (PCP) and antagonists at the glycine-site of the NMDA receptor, produce both positive and negative symptoms as well as cognitive deficits in man (Albers et al., 1999; Javitt and Zukin, 1991).

The kynurenic acid hypothesis of schizophrenia is built upon the fact that kynurenic acid is a naturally occurring astrocyte-derived antagonist at human brain NMDA- and alpha7 nicotinic- (α7nACh) receptors (Stone, 1993, 2007; Hilmas et al., 2001). The hypothesis is supported by studies showing that patients with schizophrenia display elevated levels of kynurenic acid in the CSF (approximately 1.7 nM vs. 1.0 nM in healthy volunteers; Erhardt et al., 2001a) and in the postmortem prefrontal cortex (2.9 pmol/mg protein vs. 1.9 pmol/mg protein in controls; Schwarcz et al., 2001). Kynurenic acid is a metabolite in the neuroprotective branch of the kynurenine pathway of tryptophan degradation. It is suggested that increased concentration of kynurenic acid causes alterations in glutamatergic and cholinergic, and indirectly, in dopaminergic signaling, hereby leading to symptoms of schizophrenia. In the other, neurotoxic branch of the pathway, quinolinic acid is produced. Quinolinic acid, to a large extent synthesized in microglia, is an NMDA receptor agonist (Stone, 1993).

The initial reports of increased kynurenic acid back in 2001 have since been confirmed by both post mortem and CSF studies showing elevated kynurenic acid levels in drug-treated (Sathyasaikumar et al., 2011; Linderholm et al., 2012) as well as in drug-naive patients with schizophrenia (Nilsson et al., 2005). Furthermore, kynurenine, the precursor of kynurenic acid, is also observed elevated in both CSF and cortical brain regions (Linderholm et al., 2012; Miller et al., 2006). The neurotoxic branch of the kynurenine pathway seems to be unaffected since quinolinic acid is found at normal levels in the CSF (Kegel et al., 2014) and 3-hydroxykynurenine (3-HK) levels are unaltered in the post-mortem brain (Sathyasaikumar et al., 2011; Schwarcz et al., 2001). Studies investigating peripheral levels of 3-HK detected no difference in serum levels between first-episode neuroleptic-naive patients and controls (Yao et al., 2010) whereas other studies suggested that serum levels of 3-HK are decreased following antipsychotic therapy (Myint et al., 2011, Oxenkrug et al., 2016) and could predict the severity of clinical symptoms in neuroleptic-naive patients with first-episode of schizophrenia (Condray et al., 2011). Yet another study show that basal 3-HK levels, along with increased levels of kynurenic acid, are elevated in human dermal fibroblasts obtained from individuals diagnosed with schizophrenia or bipolar disorder (Johansson et al., 2013). In addition, another metabolite of the kynurenine pathway, anthranilic acid, is markedly increased in serum of schizophrenia patients (Oxenkrug et al., 2016).

In patients with bipolar disorder, the first study showing an upregulation of the kynurenine pathway was published in 2006 when Miller and colleagues observed increased levels of both kynurenine and kynurenic acid in the post mortem anterior