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**Department of Physiology and Pharmacology**

**THE PATHOPHYSIOLOGICAL ROLES OF  
KYNURENIC ACID AND CYTOKINES  
IN PSYCHIATRIC ILLNESS**

**AKADEMISK AVHANDLING**

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## ABSTRACT

Kynurenic acid is an astrocyte-derived tryptophan metabolite and a marker of neuroinflammation that antagonizes *N*-methyl-D-aspartate (NMDA) and  $\alpha 7$  nicotinic acetylcholine receptors in the brain. Increased levels have been found in the cerebrospinal (CSF) and brains of patients with schizophrenia and experimental studies have shown that kynurenic acid bi-directionally influences dopaminergic neurotransmission. Hyperdopaminergia is suggested to underlie positive symptoms of schizophrenia and symptoms of mania/psychosis in bipolar disorder. Consistent with this notion, patients with schizophrenia show excessive amphetamine-induced dopamine release that correlates with the degree of positive symptoms. Further, patients with bipolar disorder show augmented amphetamine-induced behavioral response compared to controls. Here we examine the effects of elevated brain kynurenic acid on amphetamine-induced dopamine transmission, as well as the CSF content of kynurenic acid and cytokines in patients with bipolar disorder, in order to investigate their putative involvement in schizophrenia and bipolar disorder pathophysiology.

Accumbal dopamine release and ventral tegmental area (VTA) dopamine firing in response to amphetamine (2 mg/kg, i.p. or 0.2-25.6 mg/kg, i.v.) was measured by *in vivo* microdialysis with HPLC electrochemical detection and electrophysiology techniques. Sprague Dawley rats were treated with acute or subchronic L-kynurenine (5 mg/kg, s.c. or 90 mg/kg/day, s.c., for six days via osmotic minipumps) to elevate brain kynurenic acid levels. For locomotor activity experiments, C57BL/6 mice received acute or subchronic pretreatment of L-kynurenine (10 mg/kg, i.p. or 100 mg/kg, i.p., twice daily for six days). Spontaneous and amphetamine-induced (5 mg/kg, i.p.) locomotor activity was tested in a square open field arena.

The acute elevation of brain kynurenic acid resulted in increased anxiety-related behavior. Subchronic elevation of brain kynurenic acid produced an exaggerated amphetamine-induced accumbal dopamine release in the rat and increased locomotor activity in the mouse. These results might be related to the impaired amphetamine-induced feedback inhibition of VTA dopamine firing observed following subchronic elevation of brain kynurenic acid. Present results confirm that kynurenic acid modulates dopamine neurotransmission and behavior in rodents and that subchronic elevation of kynurenic acid is associated with dopaminergic changes that are consistent with findings in patients with schizophrenia or bipolar disorder.

Analysis of CSF showed increased levels of kynurenic acid and IL-1 $\beta$ , and decreased levels of IL-6 in patients with bipolar disorder. Positive correlations were found between the occurrence of recent symptoms of mania and the levels of IL-1 $\beta$  or kynurenic acid. Further, the lifetime occurrence of psychotic symptoms was associated with higher levels of kynurenic acid. Although causality needs to be determined, these results may suggest a pathophysiological role for IL-1 $\beta$  and kynurenic acid in psychiatric disorders involving symptoms of mania and psychosis. Given the present experimental results, prolonged elevation of brain kynurenic acid, possibly induced by increased levels of pro-inflammatory IL-1 $\beta$ , may cause a hyperdopaminergic state that drives symptoms of mania and/or psychosis. The positive correlation between CSF kynurenic acid and the dopamine metabolite homovanillic acid found in these patients further favor this idea.