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The kynurenic acid hypothesis of schizophrenia.

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Abstract

In recent years progress in the field of schizophrenia research has led to the suggestion that dopamine only plays an intermediary role in the pathophysiology of the disease and that the main abnormalities lie elsewhere. In particular, deficits in brain glutamatergic systems are suggested to play a prominent role in the pathophysiology of the disease. Kynurenic acid is an endogenous glutamate antagonist with a preferential action at the glycine-site of the N-methyl-D-aspartate-receptor. Mounting evidence indicates that the compound is significantly involved in basal neurophysiological processes in the brain. Thus, pharmacologically elevated levels of kynurenic acid, in similarity to systemic administration of phencyclidine or ketamine, were associated with increased firing rate and burst firing activity of midbrain dopamine neurons, indicating per se that elevated levels of brain kynurenic acid is associated with psychotomimetic effects. Indeed, cerebrospinal fluid level of kynurenic acid was elevated in schizophrenic patients as compared to healthy controls. The present paper also describes a prostaglandin-mediated regulation of kynurenic acid formation as well as a relationship between brain kynurenic acid concentration and the excitatory responses of ventral tegmental area dopamine neurons by clozapine and nicotine. Our results suggest that kynurenic acid contributes to the pathogenesis of schizophrenia and link the dopamine hypothesis of schizophrenia together with the idea of a deficiency in glutamatergic function in this disease.

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