

# Endogenous kynurenic acid modulates extracellular GABA levels in the rat prefrontal cortex

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A dysfunction of circuits involving prefrontal cortex (PFC)  $\gamma$ -aminobutyric acid (GABA) neurons plays an important role in the cognitive deficits seen in patients with schizophrenia (SZ) (Volk and Lewis, 2010). Another well-known pathophysiology in SZ, which may exacerbate neurotransmitter dysregulations in the disease, is the disruption of the kynurenine pathway of tryptophan degradation (Schwarcz et al., 2001). Kynurenic acid (KYNA), a product of the kynurenine pathway, is an astrocyte-derived, non-competitive antagonist of the  $\alpha 7$  nicotinic acetylcholine receptor (Hilmas et al., 2001) and, at higher concentrations, inhibits ionotropic glutamate receptors competitively. In the PFC, exogenous or endogenously formed KYNA reduces extracellular glutamate levels and impairs cognitive flexibility by blocking  $\alpha 7$ nAChRs (Alexander et al., 2012). Using microdialysis in conscious rats, we now studied the effects of KYNA (30, 100 and 300 nM) on extracellular GABA in the PFC. Applied for 2 hrs by reverse dialysis, KYNA concentration-dependently reduced extracellular GABA levels, with 300 nM KYNA causing a nadir of approximately 45% of baseline concentrations. The effects of KYNA were prevented by the co-application of galantamine (5  $\mu$ M), a positive allosteric modulator that binds at a site of the  $\alpha 7$ nAChR that is very similar to that targeted by KYNA. Galantamine did not affect GABA levels on its own. In a separate set of experiments, endogenous KYNA formation was inhibited by reverse dialysis of (S)-4-(ethylsulfonyl)benzoylalanine (ESBA; 5 mM), a specific inhibitor of kynurenine aminotransferase II, KYNA's major biosynthetic enzyme in the brain (Pellicciari et al., 2006). ESBA reversibly increased GABA levels, reaching a peak of ~160% of baseline levels. Co-infusion of 100 nM KYNA abolished the effect of ESBA on extracellular GABA, confirming the specificity of the ESBA effect. Taken together, these results indicate that fluctuations in the endogenous formation of KYNA *bi-directionally* influence extracellular GABA levels in the rat PFC. This tonic regulation, which appears to be mediated by  $\alpha 7$ nAChRs, suggests a role of astrocyte-derived KYNA in the control of PFC GABAergic neurotransmission. As cortical KYNA levels are elevated in SZ, and in light of evidence indicating reduced GABA neurotransmission in SZ, our findings suggest that drugs capable of attenuating the production of KYNA may be of benefit in the treatment of cognitive deficits in SZ.

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