Abstract tesi di dottorato: Dr.ssa Sarah Beggiato

Titolo: Endogenous kynurenic acid modulates extracellular glutamate and GABA levels in the rat prefrontal cortex and striatum: in vivo microdialysis studies.

Kynurenic acid (KYNA), a product of the kynurenine pathway (KP) of tryptophan degradation, antagonizes both the α7 nicotinic acetylcholine receptor (α7nAChR) and the glycine co-agonist (glycineB) site of the NMDA receptor (NMDAR) at nanomolar to low micromolar concentrations. As these two receptors play central roles in brain physiology and pathology, and as the concentration of KYNA in the mammalian brain may be sufficient to affect both receptors in vivo, fluctuations in endogenous KYNA levels might regulate neurotransmission and also play a role in pathological events involving α7nAChRs and NMDARs (Schwarcz et al. 2012). So far, no efforts have been made to investigate in vivo the possibility that endogenous KYNA might influence the levels of glutamate and γ-aminobutyric acid (GABA) in the striatum and in the prefrontal cortex (PFC), effects that may have significant physiological consequences and may also have implications for pathological events. In fact, a dysfunction of circuits involving PFC GABA and glutamate neurons plays an important role in the cognitive deficits seen in patients with schizophrenia (SZ) (Volk and Lewis, 2010). Interestingly, another well-known pathophysiology in SZ, which may exacerbate neurotransmitter dysregulations in the disease, is the disruption of the KP of tryptophan degradation (Schwarcz et al., 2001). Furthermore, the great majority of striatal neurons and intrinsic synapses are GABAergic, making GABA a key player in the widespread lateral inhibitory network in the region. Finally, GABAergic neurons in the human neostriatum are exquisitely vulnerable in Huntington’s disease and may be involved in the pathophysiology of SZ, two brain diseases with purported links to striatal KYNA dysfunction (Beal et al. 1990, Rassoulpour et al. 2006).

In view of above, using a microdialysis approach in awake, freely moving rats, the effects of exogenous or endogenous KYNA levels manipulations on extracellular glutamate and GABA levels in the striatum and in the PFC have been evaluated.

Applied for 2 hrs by reverse dialysis, KYNA concentration-dependently reduced extracellular glutamate and GABA levels in both brain regions, with 300 nM KYNA causing the maximal decreases. These effects were not duplicated by reverse dialysis of the selective glycineB receptor antagonist 7-CI-KYNA (100 nM) or the AMPA/kainate receptor antagonist CNQX (100 µM). On the contrary, the effects of KYNA were prevented by the co-application of galantamine (5 µM), a positive allosteric modulator that binds at a site of the α7nAChR that is very similar to that targeted by KYNA. Galantamine did not affect glutamate and GABA levels on its own in the PFC, while it moderately, but significantly, increased local striatal glutamate and GABA levels.
In a separate set of experiments, endogenous KYNA formation was inhibited by reverse dialysis of (S)-4-(ethylsulfonyl)benzoylalanine (ESBA; 1 and 5 mM), a specific inhibitor of kynurenine aminotransferase II, KYNA's major biosynthetic enzyme in the brain (Pellicciari et al., 2006). ESBA reversibly increased glutamate and GABA levels in the rat striatum and PFC, reaching a peak of ~160% of baseline levels. Co-infusion of 100 nM KYNA abolished the effect of ESBA on striatal and PFC glutamate and 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 glutamate and GABA levels in the rat striatum and PFC. This tonic regulation, which appears to be mediated by α7nAChRs, suggests a role of astrocyte-derived KYNA in the control of aminoacidergic neurotransmission in both brain areas. 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. In addition, in light of the central role of glutamate and GABA in striatal physiology, this study indicates that KYNA should be considered as an endogenous modulator of major biological functions involving the striatum, ranging from motor behavior to reward signaling and cognitive processes.

References