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Painkillers to treat schizophrenia or dementia?

Schizophrenia affects about 1 % of general population and may significantly reduce life expectancy. Drug nonadherence remains a crucial problem in the pharmacotherapy of this disorder. Animal and clinical studies results suggest that abnormal kynurenic acid (KYNA) level is involved in the pathogenesis of schizophrenia or memory impairment. Tryptophan derivative KYNA is synthesized in the brain from kynurenine (KYN) by kynurenine aminotransferases (KATs), especially by KAT II isoform. Ionotropic glutamate (GLU) receptors and α7 nicotinic acetylcholine receptors blockade are main molecular effects of KYNA.

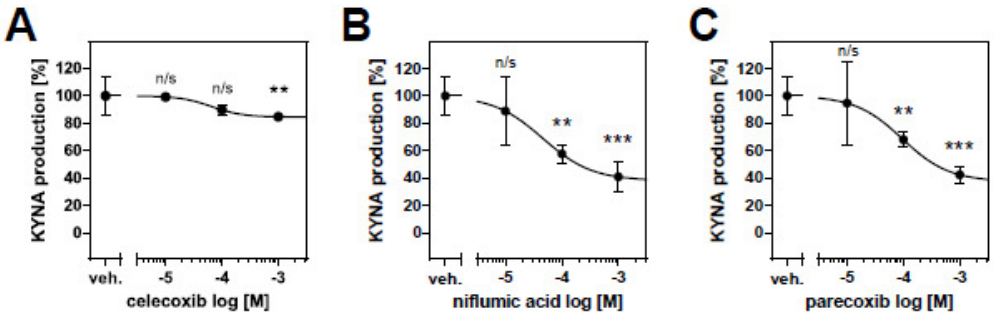

Fig. 1. Effect of celecoxib (A), niflumic acid (B) and parecoxib (C) on kynurenic acid (KYNA) synthesis in rat brain cortex in vitro.

Elevated KYNA levels have been connected with negative schizophrenia symptoms, like loss of motivation and apathy as well as cognitive dysfunction. Since inflammation and lowered glutamatergic neurotransmission are one of the main processes in schizophrenia, we analyzed the effect of anti-inflammatory agents used as popular painkillers, working as inhibitors of cyclooxygenase-2 (COX-2): celecoxib, niflumic acid and parecoxib, on KYNA production and KAT II activity in rat brain *in vitro*. The influence of COX-2 inhibitors was tested in rat brain cortex and on isolated KAT II enzyme. Niflumic acid and parecoxib in a dose-dependent manner lowered KYNA production and KAT II activity in rat brain cortex *in vitro*, whereas celecoxib seem to be ineffective.

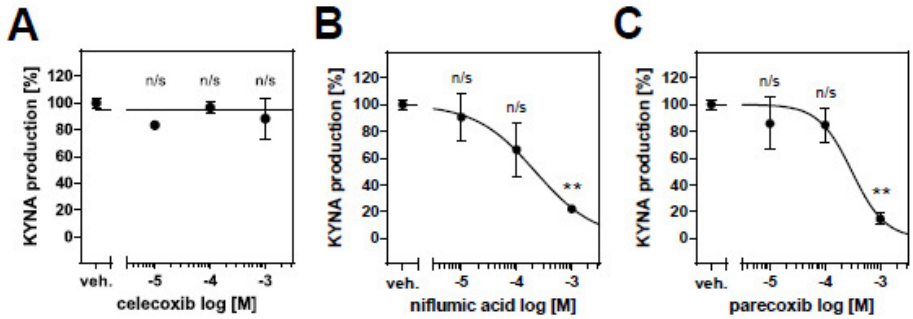

Fig. 2. Effect of celecoxib (A), niflumic acid (B) and parecoxib (C) on kynurenine aminotransferase II (KAT II) activity in rat brain cortex in vitro.

Molecular docking results suggested that niflumic acid and parecoxib affect an active site of KAT II. Concluding, niflumic acid and parecoxib are both COX-2 and KAT II inhibitors. Possible beneficial effect of tested drugs as a novel therapy of schizophrenia or cognitive decline needs further examination.

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Publication

Influence of Cyclooxygenase-2 Inhibitors on Kynurenic Acid Production in Rat Brain in Vitro.
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