Levels of Xanthurenic Acid, a Putative Activator of Type 2/3 Metabotropic Glutamate Receptors, Are Reduced in the Blood of Schizophrenic Patients and Their Healthy Relatives

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Xanthurenic acid is a metabolite of the kynurenine pathway originating from transamination of 3-hydroxykynurenine. Recent evidence suggests (but not proves) that xanthurenic acid activates mGlu2/3 metabotropic glutamate receptors in brain tissue (Copeland et al., 2013). We examined the effect of xanthurenic acid in HEK293 cells expressing mGlu2, mGlu3, mGlu4, or mGlu7 receptors. Xanthurenic acid reduced forskolin-stimulated cAMP formation in cultures expressing either mGlu2 or mGlu3 receptors (EC_{50} values = 200-400 nM), but was inactive in cultures expressing mGlu4 or mGlu7 receptors. The efficacy of xanthurenic acid at mGlu2 or mGlu3 receptors was slightly lower than the efficacy of the prototypical mGlu2/3 receptor agonist, 2R,4R-APDC. In addition, the action of xanthurenic acid was abrogated by the preferential mGlu2/3 receptor antagonist, LY341495 (1 μM). Specific [^{3}H]-xanthurenic binding could be detected in membranes prepared from mGlu2- or mGlu3-expressing HEK293 cells, but not from mock cells. However, specifically bound [^{3}H]-xanthurenic acid could not be displaced by any of the orthosteric mGlu2/3 receptor ligands, and binding of [^{3}H]-LY341495 was not affected by xanthurenic acid. Hence, we concluded that xanthurenic acid activates mGlu2/3 receptors acting as an 'allosteric agonist', i.e. displaying intrinsic efficacy at a site different from the glutamate binding site. Activation of mGlu2/3 receptors by xanthurenic acid could also be demonstrated in cultured neurons, where the drug was neuroprotective and its action was abrogated by LY341495. mGlu2 and mGlu3 receptors are involved in the pathophysiology of schizophrenia, and mGlu2/3 receptor agonists are under clinical development as novel antipsychotic drugs. We measured blood levels of xanthurenic acid in schizophrenic patients and age-matched controls by means of a HPLC/MS-MS assay that allows a reliable estimation of all metabolites of the kynurenine pathway. Using this method, we found a strong reduction in blood levels of 3-hydroxykynurenine and xanthurenic acid, and a significant increase in blood levels of anthranilic acid in a large cohort of schizophrenic patients. First-degree relatives of schizophrenic patients had levels of xanthurenic acid intermediate between those found in schizophrenic patients and healthy subjects. In contrast, blood levels of kynurenic acid were unchanged in schizophrenic patients. These data lay the groundwork for the study of xanthurenic acid in preclinical models of schizophrenia.

Copeland et al. (2013). *Neuropharmacology* 66:133-142.