

Inhibition of GABA uptake by glutamate: a novel symport mechanism.

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Investigating GABA and Glu transport inhibitory properties of novel *secoergoline* derivatives containing both GABA and glutamate bioisosteric motifs, identical effectiveness of compounds on the two distinct processes has been experienced [1]. The question arose whether this unusual lack of selectivity were related to a previously unrecognised symport mechanism that is able to transport both GABA and glutamate [1]. To explore the possibility, the effect of Glu transport inhibitors on [³H]GABA uptake was examined by the presence of the non-transportable GABA uptake inhibitor, 1-(2-benzhydrylideneaminoxyethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid (100 μM NNC-711) in rat brain homogenate to block the dominant transporter-subtype GAT1 [1]. In this pharmacologically isolated system, glutamate transporter substrates, like L-Glu, L-Asp and pyrrolidine-2,4-dicarboxylic acid (t-PDC) did partially inhibit GABA transport with IC₅₀ values in the low-micromolar range. D-Glu and D-Asp were also able to inhibit GABA uptake, but less potently than their L stereoisomers (IC₅₀ values were two-orders of magnitude higher). Glutamine showed activity similar to D-Glu and D-Asp. Non-transportable Glu uptake inhibitors (DL-TBOA, dihydrokainate), GABA transporter-family member substrates (dopamine, serotonin) and a neuropeptide co-expressing with GABA (CCK8) had no significant effect on this transport process (IC₅₀ > 1000 μM). These findings may indicate the existence of a novel GABA-Glu symport mechanism in the CNS, although it is not clear at present whether it is mediated by a known or a new transporter type.

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Reference:

- [1] L. Héja, I. Kovács I., É. Szárics, M. Incze, E. Temesváriné-Major, G. Dörnyei, M. Peredy-Kajtár, E. Gács-Baitz, Cs. Szántay, J. Kardos, *J. Med. Chem.*, 2004, 47, 5620-5629.