GET73 modulates rat extracellular hippocampal CA1 glutamate and GABA levels through a possible involvement of local mGlu5 receptor.

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N-[(4-trifluoromethyl) benzyl] 4-methoxybutyramide (GET73) is a newly synthesized compound displaying anti-alcohol and anxiolytic properties (Loche et al., 2012). In light of the importance of the hippocampal CA1 subregion in alcohol addiction and anxiety-like behaviours (Koob and Volkow, 2010), we combined *in vivo* microdialysis technique with an *in vitro* evaluation of tissue slices to characterize the effect of GET73 on glutamate and GABA levels in the rat hippocampus - including a possible role for mGlu5 receptor in mediating this effect.

Glutamate

Microdialysis results indicated that local perfusion (60 min) with 10 nM - 1mM GET73 increased extracellular glutamate levels in the CA1 region of the hippocampus of freely moving rats in a concentration dependent manner. In tissue slices from the rat hippocampus, treatment with 1 μM GET73 significantly increased K^+-evoked, but not spontaneous, glutamate efflux. In addition, 500 nM GET73, a concentration at which it is ineffective alone, partially but significantly counteracted the increase in K^+-evoked glutamate efflux induced by 100 μM CHPG, an mGluR5 agonist. Interestingly, the increase in K^+-evoked glutamate efflux induced by 1 μM GET73 was counteracted by coperfusion with a low (10 μM) concentration of the mGlu5 receptor negative allosteric modulator MPEP, which by itself is ineffective. Finally, 500 nM GET73 did not affect the reduction of K^+-evoked glutamate efflux induced by the mGluR2/3 agonist LY379268.

GABA

Both intraperitoneal administration (2-10 mg/kg) and local intra-hippocampal CA1 perfusion with GET73 (50-1000 nM) were associated with a transient, step-wise increase in dialysate hippocampal CA1 GABA levels. The GET73-induced increase in GABA levels was partially counteracted by the intra-CA1 perfusion with MPEP (300 μM). Interestingly, GET73 at the lowest (2 mg/kg) dose tested, by itself ineffective, fully counteracted the increase in GABA levels induced by the mGlu5 receptor agonist CHPG (1000 μM).

Taken together, these findings suggest that the affects hippocampal glutamate and GABA transmission. Furthermore, the present data lead to hypothesize a possible interaction between GET73 and mGlu5 receptor-mediated regulation of hippocampal CA1 glutamate and GABA levels, an effect which may be relevant to the ability of GET73 to reduce alcohol intake in an alcohol-preferring rat strain (Loche et al., 2012).

Koob and Volkow (2010). *Neuropsychopharmacology* 35, 217-38.
Loche et al. (2012). *Front Psychiatry* 3, 8.