Upregulation of mGlu2 receptors via NF-kB p65 acetylation is involved in the proneurogenic and antidepressant effects of acetyl-L-carnitine

B. Cuccurazzu[1,2], V. Bortolotto[1,2], M. M. Valente[1,2], F. Ubezio[1,2], A. Koverech[3], P.L. Canonico[2], M. Grilli[1,2]

[1]Laboratory of Neuroplasticity, Dept. of Pharmaceutical Sciences, University of Piemonte Orientale 'A. Avogadro', Novara, Italy [2]Dept. of Pharmaceutical Sciences, University of Piemonte Orientale 'A. Avogadro', Novara, Italy; [3]University of Rome Sapienza, Rome, Italy

Acetyl-L-carnitine (ALC) is a naturally occurring molecule with an essential role in cellular bioenergetics and acting as donor of acetyl groups to several proteins, including NF-kB p65. In humans, exogenously administered ALC has been shown to be effective in mood disturbances, with a good tolerability profile. No current information is available on the antidepressant effect of ALC in animal models of depression and/or the putative mechanism involved in such effect. Here we report that ALC is a proneurogenic molecule, whose effects on neuronal differentiation of adult hippocampal neural progenitors are independent of its neuroprotective activity. *The in vitro* proneurogenic effects of ALC appear to be mediated by activation of the NF-kB pathway, and in particular by p65 acetylation, and subsequent NF-kB-mediated upregulation of metabotropic glutamate receptor 2 (mGlu2) receptor expression. When tested in vivo, chronic ALC treatments could revert depressive-like behaviour caused by unpredictable chronic mild stress, a rodent model of depression with high face validity and predictivity, and its behavioural effect correlated with upregulated expression of mGlu2 receptor in hippocampi of stressed mice. Moreover chronic, but not acute or subchronic, ALC treatment increased generation of adult born neurons in hippocampi of stressed and unstressed mice. We now propose that this mechanism could be involved in the antidepressant effects of ALC in humans. These results are potentially relevant from a clinical perspective. Indeed for its high tolerability profile ALC may be ideally employed in the treatment of patient subpopulations which are particularly sensitive to side-effects associated with classical antidepressants.