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Quantification of endocannabinoids in postmortem brain of subjects with Major Depression

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The potential role of the endocannabinoid system in several mental disorders, including Major Depression (MD), has been widely discussed (Ashton CH and Moore PB, Acta Psychiatr Scand 124:250, 2011). However, little is known about the involvement of endocannabinoids (ECs) in the pathophysiology of MD. In this sense, recent studies have reported decreased serum concentrations of the main ECs, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), in depressed women relative to matched controls (Hill MN et al, Psychoneuroendocrinology 34:1257, 2009). Conversely, no changes in serum levels of the cannabimimetic compounds N-palmitoylethanolamine (PEA) and N-oleoylethanolamine (OEA) were found (Hill MN et al, Psychoneuroendocrinology 34:1257, 2009). Besides these peripheral measurements, to our knowledge, there are no published data reporting ECs levels in the brain tissue of subjects with MD.

The aim of the present study was to evaluate ECs levels in *postmortem* cerebellum (CB), hippocampus (HC) and prefrontal cortex (PFC) of subjects with MD and matched controls. Additionally, in order to investigate the potential effect of antidepressant (AD) treatment, subjects with MD were divided in two groups (AD-free and AD-treated) according to the absence or presence of AD drugs in the toxicological screening.

Brain samples were collected from patients with MD diagnosis (DSM-IV) (n=20) and were individually matched to controls (n=20) by age, gender and *postmortem* delay. ECs levels were measured by quantitative liquid chromatography with triple quadrupole mass spectrometric detection. This method was previously validated for ECs determination in human *postmortem* brain tissue (Lehtonen M et al, J Chromatogr B Analyt Technol Biomed Life Sci 879:677, 2011). The levels of four ECs (2-AG, AEA, docosahexaenoylethanolamine (DHEA) and dihomo-γ-linolenoylethanolamine (LEA)) and two cannabimimetic compounds (PEA and OEA) were measured.

In CB and PFC, no statistically significant differences were found between subjects with MD and controls for any of the ECs or cannabimimetic compounds measured. In addition, no significant differences were found between AD-free (n=7), AD-treated (n=13) and control subjects in none of the levels in CB or PCF. In HC, a statistically significant reduction in DHEA levels was found in subjects with MD respect to matched controls (-25.8%, $p<0.01$, Student´s t-test). When discriminating between AD-free and AD-treated MD subjects, DHEA levels remained significantly reduced in the HC of AD-treated subjects compared to controls (-29.1%, $p=0.02$, Dunnet´s posthoc test after one-way ANOVA). However, this decrease did not reach statistically significant values in AD-free MD subjects (-19.9%, $p=0.24$, Dunnet´s posthoc test after one-way ANOVA) respect to control group. No significant changes between control and MD groups were found in the HC for any of the other measured compounds.

These findings suggest that, at least, hippocampal levels of the endocannabinoid DHEA are decreased in MD. Moreover, AD treatment seems to be unable to restore this decrease to control levels.