Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue1abst037.pdf

Effects of acute and repeated administration of escitalopram and FAAH inhibitor on the level of endocannabinoids and endocannabinoid-like molecules in different rat brain structures

Irena Smaga[1], Beata Bystrowska[1], Irmina Turek[1], Małgorzata Filip[1,2]. [1]Department of Toxicology, Faculty of Pharmacy, Jagiellonian University, Medical College, Kraków, Poland, [2]Laboratory of Drug Addiction Pharmacology, Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland

Depression as one of the major lifestyle diseases of the twenty-first century is a serious therapeutic problem in modern pharmacotherapy. In recent years there has been highlighted the potential participation of the endocannabinoid system in the pathogenesis of depression and in the action of antidepressants.

The aim of this study was to investigate the effect of the clinically effective antidepressant escitalopram (ESC, funded by Lundbeck) and of the fatty acid amide hydrolase (FAAH) inhibitor (URB597), showing antidepressant activity in preclinical studies, on the level of endocannabinoids anandamide (AEA) and 2-arachidonylglicerole (2-AG) as well as of endocannabinoid-like molecules palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) in different rat brain structures.

Male Wistar rats received vehicle or drugs intraperitoneally (ESC, 10 mg/kg, or URB597, 0.3 mg/kg) for 14 days or only acutely on day 14th followed by 13 days of vehicle injections. ESC was dissolved in sterile 0.9% NaCl (pH of an ESC solution has been neutralized with 10% NaOH solution). URB597 was dissolved in 2-3 drops of ethanol and diluted as required in a 1% aqueus solution Tween 80. N=8 rats/group. Twenty four hours after the last injections the animals were decapitated and the tissue levels of lipid-based molecules were determined with using the liquid chromatography mass spectrometry. Data were analyzed by using one-way ANOVA followed by the Dunnett's test.

Administered acutely ESC resulted in decreased levels of 2-AG ($p<0.05$), PEA ($p<0.001$) and OEA ($p<0.01$) in the frontal cortex and of OEA ($p<0.05$) and PEA ($p<0.01$) in the cerebellum while PEA levels ($p<0.05$) in the hippocampus were increased. Single administration of URB597 increased the striatal 2-AG ($p<0.05$) levels and decreased PEA ($p<0.01$) and OEA ($p<0.05$) levels in the hippocampus. On the other hand, chronic administration of either ESC or URB597 resulted in paralleled increases in levels of AEA ($p<0.05$) and of 2-AG ($p<0.05$) in the hippocampus and dorsal striatum while enhancement in PEA levels in the hippocampus ($p<0.001$) was detected following ESC or in the prefrontal cortex ($p<0.001$) and cerebellum ($p<0.05$) following URB597. At the same time, chronic ESC decreased 2-AG, OEA or PEA levels in the cortical structures (2-AG and OEA: $p<0.01$; PEA: $p<0.001$) and cerebellum (2-AG: $p<0.05$; OEA and PEA: $p<0.001$) and chronic URB597 reduced 2-AG levels ($p<0.05$) in the frontal cortex and PEA/OEA levels (PEA: $p<0.01$; OEA: $p<0.05$) in the hippocampus.

Our present data, showing increased levels of AEA and of 2-AG in the hippocampus and dorsal striatum, together with recent observation on imipramine (Smaga et al., Pharmacol. Rep., 2011), give rise to the endocannabinoid hypothesis of depression.

Acknowledgements: This study was supported by the research grant UMO-2012/05/B/NZ7/02589 from the National Science Centre, Kraków, Poland.