Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue1abst051.pdf

Changes in levels of endocannabinoids and endocannabinoid-like molecules in the selected rat brain structures during cocaine relapse.

Beata Bystrowska[1], Irena Smaga[1], Ewa Nowak[2], 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

Recent preclinical behavioural reports indicate that endocannabinoids such as anandamide (AEA) or 2-arachidonoylglycerol (2-AG) as well as other non-cannabinoid lipid signaling molecules, such as oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) are important regulators of addiction processes. AEA and 2-AG are ligands for cannabinoid receptors while AEA, OEA and PEA activate TRPV1 and PPAR-α receptors. By substrate competition, OEA and PEA reduce AEA metabolism while PEA also inhibits rate of AEA metabolism by suppression of the fatty acid amide hydrolase (an enzyme blocking the degradation of AEA, OEA and PEA) expression.

The aim of this study was to evaluate the role of endocannabinoid system in cocaine addiction. We focused on the brain tissue levels of AEA, 2-AG, OEA and PEA in several brain regions during drug-induced relapse in rats.

32 Male Wistar rats (280–300 g) were trained to self-administer cocaine (0.5 mg/kg/infusion) followed by extinction training (no access to cocaine) and relapse evoked by cocaine priming dose (10 mg/kg, ip). To generate a control group (n=8) and 3 studied groups (n=8), a “yoked” triad procedure was used [Frankowska M. et al. Pharmacol Rep. 2009]. After completion of behavioral experiments the brain structures were isolated: the nucleus accumbens (NAC), dorsal striatum (STR), prefrontal cortex (PFC), frontal cortex (FG), hippocampus (HIP) and cerebellum (CER). Separation of lipid-based molecules were performed on a reversed- phase HPLC system (Agilent 1100 series, Agilent Technologies) using a Thermo BDS HYPERSIL C18 column (3μm particle size, 100x3mm) at a flow rate of 0,3ml/min. Mass spectrometric detection was performed using a mass spectrometer (API 2000, Applied Biosystems) with an electrospray (ESI) ion source. Data were analyzed by using one-way ANOVA followed by the Dunnett’s test.

We found a statistically significant ($p<0.0001$) decrease of the AEA level in the NAC ($\bar{x}$=7.61 ± 0.76 ng/g) and CER ($\bar{x}$=2.89 ± 0.20 ng/g) in groups of animals with a history of cocaine intake either active or passive, and an increase in the HIP ($\bar{x}$=9.57 ± 0.44 ng/g; $p=0.002$) only in animals self-administered cocaine. During cocaine relapse, the level of 2-AG increased in the HIP ($\bar{x}$=11.46 ± 0.77 μg/g; $p<0.0001$) and NAC ($\bar{x}$=5.17 ± 0.36 μg/g; $p<0.0001$) while a reduction in the FC ($\bar{x}$=3.026 ± 0.24 μg/g; $p<0.001$) was seen in rats previously self-administered cocaine. In the “yoked” cocaine group an increase of 2-AG was reported in the STR ($\bar{x}$=8.62 ± 0.64 μg/g; $p<0.0001$). Moreover, drug-induced relapse resulted in a potent increase ($p<0.0001$) in OEA levels in the PFC ($\bar{x}$=55.96 ± 2.5 ng/g) and STR ($\bar{x}$=151.8 ± 11.29 ng/g) and in PEA in the PFC ($\bar{x}$=151.3 ± 5.16 ng/g), FC ($\bar{x}$=128.2 ± 5.5 ng/g) and STR ($\bar{x}$=138.3 ± 7.3 ng/g), while a decrease ($p<0.0001$) in the NAC (OEA: $\bar{x}$=18.65 ± 2.14 ng/g; PEA: $\bar{x}$=22.79 ± 2.3 ng/g) and CER (OEA: $\bar{x}$=17.99 ± 2.27 ng/g; PEA: $\bar{x}$=19.13 ± 2.02 ng/g) was noted.

To summarize, the present findings support a role for endocannabinoids and endogenous N-acyl ethanolamines to control drug relapse in rats. Our results support some behavioral analyses with using cannabinoid, TRPV1 or PPAR-α receptor ligands to control drug addiction.

Acknowledgements: This study was supported by grant NN404273040 by the Ministry of Science and Higher Education Warszawa, Poland.

References:

Adamczyk et al., J Physiol Pharmacol 60, 119-25, 2009

Oz Murat et al. J. Neurochem 112, 1454-1464, 2010

De Petrocellis et al.: Best Practise&Res. Clin. Endocrinology&Metab 23, 1-15, 2009