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LONG-TERM EFFECTS OF ENDOCANNABINOIDS DEPENDENT SYNAPTIC PLASTICITY IN MICE EXPOSED TO INTERMITTENT ALCOHOL DURING ADOLESCENCE

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Alcohol drinking, especially among adolescents and young adults, is a serious public health concern. Ethanol interacts with the endocannabinoid system (ECS) whose function may be altered in ethanol dependence. Here, we investigated the effect of ethanol consumption on excitatory synaptic transmission and plasticity mediated by the cannabinoid CB1 receptor in dentate gyrus (DG). Male C57BL6 mice were exposed to intermittent ethanol intake (20% (v/v) in tap water) using a 4 days drinking-in-the-dark procedure during adolescence (PD 30 to 54). Animals were given access to ethanol (or water) for 2h sessions during 3 days, and 4h session on the 4th day. At 18-21 days withdrawal from ethanol, adult mice were sacrificed. Electrophysiological, immunohistochemical, and molecular techniques were applied. Excitatory postsynaptic potentials (fEPSPs) were evoked after stimulation of the medial perforant path and recorded in the supragranular zone of the dentate molecular layer (ML) in the presence of the GABAA antagonist picrotoxin. CB1 activation by CP55,940 (10μM) inhibited fEPSPs in controls (26.43±2.77% of baseline) as already shown. However, this effect was not observed in ethanol-exposed mice (4.9±7.47% of baseline). Furthermore, ML synaptic stimulation (10min, 10Hz) triggered a long term depression (LTD) of the excitatory transmission that was absent in adult mice after ethanol consumption during adolescence (2.7±3.12% of inhibition; $p<0.0001^{***}$). This plasticity was CB1 dependent as the AM251 antagonist (4μM) abolished LTD (8±6.6% of inhibition). CB1 immunoreactivity decreased in ML of ethanol-exposed (87.47±0.58%) vs control (100±0.77%) mice. Also, the relative mRNA and CB1 protein significantly decreased, while a significant increase in MAGL (mRNA and protein) was detected. Altogether, repetitive exposure to ethanol during adolescence leads to a deficit of endocannabinoid-dependent LTD in adult DG excitatory synapses, probably due to a down-regulation of CB1 receptors and a reduction of the endocannabinoid tone by an increase of MAGL.