EVIDENCE FOR A POSSIBLE INTERACTION BETWEEN CANNABINOID AND SEROTONERGIC SYSTEMS IN MODULATING INHIBITORY SYNAPTIC TRANSMISSION IN BASOLATERAL AMYGDALA

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Endocannabinoids are important neuromodulators involved in several functions such as analgesia, cognition and emotional behaviour. In the brain, the cannabinoid receptor 1 (CB1) is highly expressed on GABAergic neurons and recently, functional CB1 were identified on glutamatergic terminals (1, 2). By activation of CB1, the endocannabinoid exert important functions such as retrograde inhibition of neurotransmitter release and regulation of long-term synaptic plasticity. To investigate the role exerted by CB1 expressed on different neuronal types on synaptic transmission, we used conditional mutant mice in which CB1 are deleted in all principal neurons but not in the majority of GABAergic interneurons ($CB1^{f/f;CaMKII\alpha Cre}$), and mutant mice in which the receptor is deleted in GABAergic neurons only ($CB1^{f/f;Dlx\ 5/6Cre}$). In addition, we performed experiments in conditional mutant mice lacking CB1 receptors only in glutamatergic cortical neurons ($CB1^{f/f;Nex\text{-}Cre}$) but not in the other neurons (serotonergic, cholinergic, GABAergic). Whole-cell patch clamp recordings were performed in coronal brain slices of conditional mutant mice. Electric stimuli were delivered to the lateral amygdala to evoke inhibitory postsynaptic currents (IPSCs) in the basolateral amygdala (BLA). We found that the CB1 agonist Win55, 212-2 (WIN, 5 µM), reduced IPSC amplitude in wild type (wt) mice (65.6 ± 9.4 % of baseline) but surprisingly, it failed to affect IPSC in $CB1^{f/f;CaMKII\alpha Cre}$. In addition, in $CB1^{f/f;Dlx\ 5/6Cre}$ mice WIN was still able to reduce IPSCs (84.3 ± 1.2 % of baseline). The effect of WIN on IPSC was not different between $CB1^{f/f;Nex\text{-}Cre}$ (62.0 ± 4.5 %) and their respective wt mice (57.3 ± 5.6 %). These results suggest that the effect of WIN in reducing IPSC in BLA is not mediated solely by CB1 expressed on GABAergic terminals. In GABAergic neurons of the BLA, CB1 are co-expressed with serotonergic 5-HT_3 receptors. We found that the 5-HT_3 receptor antagonists, MDL72222 (20 µM) and Ondansetron (OND, 20 µM) reduced the frequency of spontaneous and miniature IPSC. Furthermore, OND reduced IPSC amplitude in a concentration dependent way (IC_{50}Ond=12.9µM) and its concentration-response curve was shifted to the left in the presence of 5 µM Win (IC_{50} Ond+WIN=3.7µM). Interestingly, in $CB1^{f/f;CaMKII\alpha Cre}$ WIN did not modify the concentration-response curve for OND (IC_{50}Ond = 16.5µM, IC_{50}Ond+WIN = 15.4µM). These findings suggest that CB1 and 5-HT3 receptor functionally interact in the BLA in modulating inhibitory synaptic transmission.

1) Monoroy K et al. 2006, Neuron 51:455-66. 2) Domenici et al. 2006, J Neurosci 26:5794-9.