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A novel role of cannabinoids in synaptogenesis

Sara Hamzeh
University of Montreal, Canada

Synapses play a major role in signalling transduction in the nervous system. They display extensive activity-driven plasticity during development, learning and memory. Here we have explored a new role of endogenous cannabinoids and their CB1 receptor in synapse formation, remodelling, and maintenance. Endogenous cannabinoids and their CB1 receptors have been known to regulate neurotransmitter release at the level of the synapse and have also been implicated in several developmental events. Recently, it was reported that endogenous cannabinoids decrease functional synapses in pyramidal neurons. We show here that endogenous cannabinoids and their CB1 receptors regulate the dendritic and axonal filopodia formation (synapse precursors) and synaptogenesis in embryonic mouse cortical cultures. Stimulating the cortical cultures with synthetic CB1 receptor agonist, arachidonyl-2'-chloroethylamide (ACEA), showed a significant decrease in filopodia number at DIV8, and subsequently a lower synaptic contact density at DIV10 compared with the control group. On the other hand, inhibiting the action of endogenous cannabinoids and their CB1 receptors by the inverse agonist AM251 or by the pure antagonist O2050 increases filopodia density at DIV8, and elevates synaptic density formation at DIV10 . Furthermore, we found that this increase was reversed when cultures were pre-treated with H89, KT5720 (both inhibitors of Protein Kinase A(PKA)) or DCCfb antibody, (an antibody which blocks the function of Deleted in Colorectal Cancer Receptor). Interestingly, a decrease of DCC receptors present at the surface of the neurons was observed when treated with ACEA. Conversely, an increase of DCC was observed when CB1 receptors were inhibited by AM251 or O2050 and this effect was prevented when neurons were pretreated using H89, KT5720.This confirmes the previous observations showing that the activation of adenylate cyclase and PKA pathway produced a netrin-1-DCC dependant increase in synaptogenesis. In order to verify the putative link between cannabinoid and netrin-1 systems, we performed *in vitro* experiments on primary cortical neurons obtained from dcc knockout mouse embryos. In the absence of the DCC receptor, the inverse agonist AM251 and the antagonist O2050 showed no increase in axonal and dendritic filopodia, or synapse density confirming a connection between the two systems in the underlying mechanisms of synapse formation. We propose that endocannabinoids acting on their CB1 receptors, decrease cytosolic cAMP concentration and inhibit PKA. This blocks the recruitment of the DCC receptor to the membrane surface and therefore, inhibits the action of netrin-1 regulating synaptogenesis. In this study, we show that an interplay between the endogenous cannabinoids and the DCC / netrin-1 pathway regulates synapse formation during neural development. These findings indicate a profound role of endogenous cannabinoids and a breakthrough in understanding the mechanisms implicated in synaptogenesis.

Biography

Sara Hamzeh hold a masters'degree in Pharmaceutical Sciences from Univerity of Montreal in Canada with a Thesis and have extensive experience with multinational Pharmaceutical companies. She has knowledge and familiarity of different types of industries (Healthcare, Veterinary, Pharmaceutical and Medical). She has been a member of many organizations such as the PDA, Parenteral Drug Association Chapter of Canada.

sarahamzeh@hotmail.com

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