Module 9: Neurodegeneration (II) by Arghya Sharma Date:10/30/21

The author is trying to illustrate the relationship between the increase in synaptic activity and aggregation of amyloid beta peptide (over a long period of time). As we have learned in the lecture, according to the APP hypothesis amyloid beta peptide induces the formation of neurofibirilation tangles, which will lead to neuronal and synaptic loss that will have a direct impact on memory and working of the brain.

In this experiment, the technique of optogenetics is used to stimulate neuronal activity of the perforant pathway neurons. In this experiment SSFO which is short for stabilized step function opsin is used. SSFO is a channelrhodopsin that has the ability to produce sub-threshold membrane potential changes that can last many minutes, it also has a high sensitivity to light and enables non-invasive light-induced activation of SSFO-expression neurons. In order to target opsin expression to specific neuronal projections in the LEC and DG a virus (in this case adeno-associated Virus) under the control of a promoter (CaMKIIα is used because it is biased towards excitatory cells in cortical region) is used to express the opsin. Two types of AAV vectors are incorporated in the coronal section. One is composed of the virus, and the opsin (SSFO) combined with yellow green fluorescent protein (EYFP) and the other is AAV-EYFP. For unilateral optogenetic stimulation of neurons in the dentate gyrus (DG) and the lateral entorhinal Cortex, it seems like immunofluorescence labeling of the c-Fos and the YFP is done in the coronal section of the mice infected with the AAV-SSFO-EYFP or AAV-EYFP. C-Fos is specifically labelled because c-Fos can be used to determine the activity in neurons and neuronal circuits after a variety of stimuli. According to my understand, when using light stimulation on AAV-SSFO infected mice there was an increase in the neuronal activity in the ipsilateral side of the LEC and DG compared to the contralateral side of LEC & DG in the AAV-SSFO-EYFP infected mice- this is illustrated in the first figure with red dots that represent stained C-fos being expressed as a sign of neuronal activity: pictures B to E. In the AAV-EYFP infected mice, light stimulation in only modest levels of c-fos activity (not much fluorescence detected) which means neuronal activity is not detected. FIgure 2 further strengthens the understanding of the author from the previous picture. It shows the light stimulation leads to increase in levels of interstitial fluid of Aβ42 in the hippocampus of SSFO infected APP Tg mice and in comparison was significantly higher than that for mice infected with EYFP.

In conclusion, through this experiment it can be verified that increase in synaptic activity leads to increase in Aβ42 in the hippocampus. As discussed before, Aβ peptide is considered as one of the causes for alzheimers.

Citations:

[1] E;, B. (n.d.). *Expression of c-fos-like protein as a marker for neuronal activity following noxious stimulation in the rat*. The Journal of comparative neurology. Retrieved October 30, 2021, from https://pubmed.ncbi.nlm.nih.gov/2113539/.

[2] Kim, C. K., Adhikari, A., & Deisseroth, K. (2017, March 17). *Integration of optogenetics with complementary methodologies in Systems Neuroscience*. Nature reviews. Neuroscience. Retrieved October 30, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5708544/v.

[3] Tye, K. M., & Deisseroth, K. (2012, March 20). *Optogenetic investigation of neural circuits underlying brain disease in animal models*. Nature reviews. Neuroscience. Retrieved October 30, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6682316/.