Melatonin receptor agonist ameliorates PTSD-like behaviors in *Fabp3*$^{-/-}$ mice

Yasushi Yabuki[1,2], Kazuya Matsuo[2], Yuji Owada[3], Norifumi Shioda[1], Kohji Fukunaga[2]

[1]Dept. Genomic Neurology., IMEG., Kumamoto Univ., [2]Dept. Pharmacol., Grad. Sch. Pharm., Tohoku Univ, [3]Dept. Org Anato., Grad. Sch. Med., Tohoku Univ.

Fatty acid binding proteins (FABPs) are required for long-chain polyunsaturated fatty acids (LCPUFAs) intracellular trafficking, uptake, transport and metabolism. Whereas FABP3, FABP5 and FABP7 are expressed in the brain of mice and humans, FABP3 is predominantly expressed in the mature neurons. Previous clinical studies reported that supplementation of LCPUFAs relieves post-traumatic stress disorder (PTSD) symptoms. Here, we investigated relationship between PTSD-like symptoms and FABP3. FABP3 null (*Fabp3*$^{-/-}$) mice showed cognitive deficits, hyperlocomotion and impaired fear extinction as PTSD-like behaviors. We observed significantly reduction of calcium/calmodulin-dependent protein kinase II (CaMKII) autophosphorylation in the anterior cingulate cortex (ACC) of *Fabp3*$^{-/-}$ mice. By contrast, elevated CaMKII autophosphorylation and c-Fos expression levels were observed in the basolateral amygdala (BLA) after exposure to contextual fear conditions. Interestingly, Melatonin receptor (MTR) agonist ramelteon (1.0 mg/kg, p.o.) antagonized abnormal c-Fos expression and CaMKII autophosphorylation levels in the ACC and BLA, resulting in improvement of PTSD-like behaviors in *Fabp3*$^{-/-}$ mice. MTR antagonist luzindole (2.5 mg/kg, i.p.) inhibited the effect of ramelteon. Since melatonin receptors are few expressed in the amygdala, we suggest that ramelteon may restore decreased neuronal activity in ACC via MTR activation and in turn ameliorate aberrant BLA activity, thereby improving PTSD-like behaviors in *Fabp3*$^{-/-}$ mice.