

*Functional changes in the dopaminergic ventral tegmental area in the three hit model of depression*

Worldwide 350 million people are affected by depression. Functional abnormalities in monoaminergic systems are proven, although antidepressant treatment on monoamines in 30% remains ineffective. The ventral tegmental area (VTA) is a center of mesocorticolimbic dopaminergic system involved in mood control and depression. The three hit concept is a commonly used model for major depression: co-occurring genetic, epigenetic and acquired stress factors precipitate the symptoms. Our research team developed a model by combining the lack of the PACAP gene (genetic factor), maternal deprivation (epigenetic factor) and chronic variable mild stress (CVMS) (acquired factor). We hypothesized that the expression of the neuronal activation marker FosB, in tyrosine-hydroxylase (TH) neurons of VTA, will be affected both by our model and by antidepressant (i.e. fluoxetine) treatment. To test our hypothesis litters of PACAP heterozygous mice were divided into main groups based on quality of maternal care. Offspring was subdivided into control and CVMS groups. Half of mice received either saline or fluoxetine injections. Indirect immunolabeling for FosB and TH was performed.

Results showed that both maternal deprivation and the fluoxetine significantly increased FosB neuronal activity, but CVMS remained ineffective. The efficacy of fluoxetine in the VTA was stress-level dependent. The double-labeling proved that the effects were specific for TH immunoreactive neurons.

In conclusion, animals with all risk factors showed elevated neuronal activation in the VTA, which was not reversed by fluoxetine treatment. This suggests that our model may help to study the therapy resistant depression cases.