Serotonin plays an important regulatory role in neuronal proliferation, migration and differentiation during brain development. Depletion or excess of 5-HT during pre- and postnatal development results in structural and functional abnormalities within the cortex and hippocampus. There is evidence that prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) may be associated with a higher risk of autism spectrum disorder (ASD) in later life, characterized by sensory and perceptual dysfunctions including no interest in interactions with others and difficulties in social interactions as well as repetitive behavioral patterns. Disturbances of the serotonergic system, which controls a spectrum of physiological and cognitive processes in the adult organism, have also been described in ASD, however, little is known about the effects of perinatal exposure to SSRIs on the development and functions of the serotonergic system. We hypothesize that perinatal exposure of mice to a SSRI, fluoxetine, will result in disturbances in the structure and function of neurons, the neuronal network and serotonergic projections originating from the dorsal raphe nucleus (DRN), one of a main sources of the serotonergic innervation of the forebrain.

In the first phase of the project the influence of the exposition of mice during pregnancy and lactation to fluoxetine, on the structure and functions of different types of DRN neurons of the male and female offspring will be investigated using electrophysiological and immunohistochemical methods. The influence of perinatal fluoxetine on the offspring will also be assessed using behavioral tests. The first phase of the project will be completed by determining the characteristics of identified DRN neurons in Fmr1 KO mice, a model of human Fragile X Syndrome resulting in ASD. In the second phase of the project an attempt to ameliorate the influence of perinatally administered fluoxetine on DRN neurons by co-administration of the 5-HT_7 receptor antagonist SB 269970 will be conducted. Planned experiments also involve administration of a new generation antidepressant vortioxetine, which acts as an antagonist of the 5-HT_7 receptor, to test whether it can replace fluoxetine treatment without the harmful effects on the offspring phenotype. The second phase of the project will be completed by determination of the characteristics of identified DRN neurons in 5-HT_7 receptor KO mice.

Completion of the proposed studies will provide new insights into neuronal mechanisms underlying perinatal SSRI-induced abnormalities in DRN function and a possible involvement of the 5-HT_7 receptor in these processes. It is expected that the results will contribute to a better understanding of the functioning of the brain serotonergic system and its disturbances, which may be related to the pathophysiology of autism spectrum disorders. The results may indicate new directions of research aimed at finding ways to counteract unwanted side effects of antidepressant therapies.