Stress is an inherent aspect of life. In response to stressors organism runs a number of processes to deal with a stressful situation and ensure the proper functioning of the body. Two main stress responses can be distinguished. The first, fast stress response is connected with activation of the sympathetic nervous system, which triggers the fight-or-flight response. The second, slower phase of a reaction is related to the activation of the hypothalamic – pituitary – adrenal (HPA) axis. This response is characterized by release of corticotropin-releasing hormone (CRH) from parvocellular neurons of the paraventricular nucleus of hypothalamus (PVN). When CRH binds to CRH receptors on the anterior pituitary gland, adrenocorticotropic hormone (ACTH) is released from corticotropes. ACTH binds to receptors on the adrenal cortex and stimulates adrenal release of glucocorticoids, called stress hormones. The HPA axis is regulated by a negative-feedback loop, and its proper functioning plays a crucial role in limiting the stress response. The increase in the concentration of glucocorticoids leads to inhibition of the hypothalamus and pituitary, resulting in stopping further release of glucocorticoids from the adrenal glands. The negative effects of stress occurs when stress is prolonged or too strong and exceeds the body's ability to cope with it. Prolonged chronic stress causes an increase in the level of stress hormones and interferes with the normal regulation of the HPA axis, which leads to the formation of different kinds of disorders. Strong or prolonged stress is considered as a risk factor in the development of affective disorders including depression or schizophrenia.

An increasing body of recent evidence indicates that especially early life stress can have long-lasting detrimental consequences. It can affect brain development and results in physical, behavioral and cognitive alterations in childhood and adulthood. Prenatal stress may be involved in the pathogenesis of psychiatric disorders and increases susceptibility to depression and schizophrenia. In experimental studies appropriate animal models are used to best explore the mechanisms of action of stress on the maturing brain. The prenatal stress procedure described in this research project is one of the well characterized animal models of depression. In this model female rats are subjected to stress during pregnancy and the effects of stress are observed in the adult offspring. Prenatal stress causes changes in a wide range of brain structures, including the frontal and prefrontal cortex, hippocampus and amygdala. The proposed project aims to determine how prenatal stress affects the proper functioning of the other structure of the brain - the dorsal raphe nucleus.

The dorsal raphe nucleus (DRN) is the main source of serotonin (5-HT) within the brain. It is involved in a variety of physiological and cognitive processes including sleep, learning and memory, temperature regulation, appetite, blood circulation and heart rate. The DRN also plays a crucial role in mood regulation and stress responses. Abnormalities in the serotonergic system have been implicated in the pathophysiology of mood disorders, including depression. The DRN projects to a wide range of brain structures and receives inputs from them. DRN cells release not only 5-HT but also glutamate, GABA, dopamine and other neurotransmitters. The activity of neurons within the DRN is modulated by local connections and also by projections originating from other brain structures, which makes the organization of the neuronal network within the dorsal raphe nucleus complex and largely unknown. Impact of prenatal stress on the functions of DRN neurons is still far from being fully understood. The main aim of the present project is to investigate the effects of prenatal stress on the functions of DRN neurons and excitatory (glutamatergic) and inhibitory (GABAergic) synaptic inputs to these cells using electrophysiological recording techniques. The determination of these changes in the proposed project will contribute to the understanding of the mechanisms of prenatal stress and its impact on the development of mood disorders.

The effects of maternal stress are observed both in the mother and the fetus. This kind of stress leads to alterations in activity of the HPA axis. In response to stressor maternal HPA axis is activated, which increases levels of CRH and glucocorticoids. This, in turn, increases the production of placental CRH and leads to the hyperactivation of the HPA axis of the fetus. In prenatally-stressed animals changes in CRH and CRH receptors have been observed in different brain structures e.g. the amygdala and hypothalamus. An increased susceptibility to behavioral and mood disorders may be caused by changes in functioning of the HPA axis. Corticotropin-releasing hormone regulates the stress response but it also plays a very important role in regulating the activity of DRN neurons and serotonin release. CRH acts via CRF_1 and CRF_2 receptor subtypes expresed in the serotonergic and GABAergic neurons within the DRN and modulates 5-HT release. Planned experiments will determine how prenatal stress disrupts functions of corticotropin-releasing hormone within the DRN. Moreover, activation or blockade of CRH receptors using the appropriate agonists and antagonists will answer the question of which CRH receptor subtypes may be involved in these changes.

Because prenatal stress is considered as a risk factor in the development of affective disorders, the last aim of this project is to reverse the adverse effects of prenatal stress in the dorsal raphe nuclei. For this purpose antagonist of $5\text{-}HT_7$ receptor - SB 269970 will be used. The $5\text{-}HT_7$ receptor is one of serotonergic receptors, which has been implicated in pathophysiology of depression and anxiety. Antagonists of $5\text{-}HT_7$ receptor represent interesting new group of compounds having antidepressant activity. It has been shown, that blocking the $5\text{-}HT_7$ receptor by the administration of SB 269970 reverses negative effects of stress on excitatory neurotransmission and synaptic plasticity in the rat frontal cortex. Current treatment of affective disorders is not fully effective and requires prolonged administration of the drug. Further studies aimed at understanding the exact mechanisms of adverse effects of stress on the nervous system are extremely important. The results obtained in this research project will help to better understand the mechanism of prenatal stress-related changes in functions of DRN neurons and, in the future, they may contribute to the development of new, more effective therapies of diseases related to stress.