Summary

Abuse of psychoactive substances poses a serious threat to public health. Novel psychoactive substances (NPS), generally known as “designer drugs”, appeared around the half of the first decade of the 21st century being a cheap and legal alternative to internationally scheduled drugs of abuse. Synthetic cathinones are the second largest and most prevalent group of NPS. They have similar chemical structures to classic psychostimulants, such as MDMA (“ecstasy”) or methamphetamine, as well they display the same mechanism of action – potentiation of brain signaling by elevating levels of monoamine neurotransmitters i.e., dopamine, noradrenaline and serotonin in the synaptic cleft. 3,4-Methylenedioxypyrovalerone (MDPV) is a synthetic cathinone with particularly potent dopaminergic activity, abuse of which frequently results in severe symptoms of intoxication linked to neurotoxicity that can even be lethal.

Negative impact of classical psychostimulants was observed in children of women abusing them during pregnancy. Exposure to classical psychostimulant drugs of abuse during development of the central nervous system induces impairment of memory in young and adult animals. It is known that learning and memory are associated with generation of new neurons and synaptic connections in a specific region of the hippocampus – the dentate gyrus (DG). However, the neurobiological mechanisms underlying distant aftermaths of exposure to psychostimulants during neurodevelopmental stage are complex and not fully resolved. At the moment, the data on long-term consequences of neurodevelopmental exposure to synthetic cathinones is scarce.

This dissertation aims to assess the effects of MDPV, administered to mice on postnatal days 11 to 20 (PD11-20), on development and functioning of the hippocampus as well as on memory of adult animals. The selected period corresponds to the 3rd trimester of human pregnancy in terms of the crucial time for hippocampal development. In the experiments mice of both sexes were used, to find out if neurotoxicity of MDPV is sex-dependent.

Male and female C57BL/6J inbred mice at the age of PD11-20 were injected subcutaneously, twice a day, with MDPV (10 or 20 mg/kg of body weight) or saline.

Additionally, mice were injected subcutaneously, once a day, with bromodeoxyuridine (BrdU) – a marker of cell proliferation. After reaching adulthood, at the age of 12 weeks, mice underwent the assessment of various types of memory with complementary behavioral tests. Working spatial memory was measured with Y-maze spontaneous alternation test, short- and long-term recognition memory with novel object recognition test after 3- and 24-h retention time, while spatial learning and memory as well as reference memory with Morris water maze (MWM) paradigm. After completion of behavioral testing, mouse brains were isolated for assessment of neurogenesis in the DG by identification of BrdU-labeled cells, and for assessment of synaptic plasticity of the hippocampus by measurement of synaptophysin (SYP) and postsynaptic density protein (PSD95) expression with Western blot.

It has been revealed that postnatal exposure to MDPV resulted in impairment of working spatial memory as well as short and long-term recognition memory. However, MDPV did not disturb hippocampal-dependent learning, spatial memory and reference memory, what was confirmed by a lack of impairment of neurogenesis in the DG and synaptic plasticity in the hippocampi of animals. During MWM test, in some mice treated with 20 mg/kg MDPV episodes of floating occurred, what might be caused by worsened tolerance to chronic stress experienced by mice while swimming. All observed MDPV effects on mouse behavior were sex-independent. Although behavioral and molecular analysis indicate a lack of developmental and functional impairment of the hippocampus, the observed impairment of working spatial memory and recognition memory might be caused by disturbed functioning of structures functionally connected with the hippocampus. However, further investigation is required to verify these hypotheses.

In conclusion, exposure to MDPV during the development of the central nervous system in mice induces memory impairments in adulthood. The results presented in this dissertation might contribute to determination of the harmful mechanism that MDPV exerts on a developing brain and help to estimate the risk associated with abuse of synthetic cathinones during pregnancy.