

The undertaking of the planned research was inspired by our recognizing the timeliness of it - in that there is a growing worldwide problem of consumption of new psychoactive substances (NPS), commonly known as "boosters", and risks associated with the abuse of these drugs. NPS are mainly used by young people, and their consumption may lead to the development of many disorders in adulthood. Among these are: learning disorders and memory deficits and tendency to abuse different psychoactive substances. Likewise, boosters poisonings are a growing problem and concern especially within the young.

One of the most abused NPSs is mephedrone (4-MMC, 4-methyl methcathinone) - a synthetic derivative of cathinone. This drug has been known since 2009, and is extensively abused. The effects of taking mephedrone include: agitation, euphoria, racing thoughts and dreams, as well as sleeplessness and restlessness. However, its physiological effects on the body are not exactly known. In addition to the recognized somatic symptoms and the euphoric effect of mephedrone, it can induce a number of side effects, ranging from tremor of the hands, to psychiatric disorders, especially in the case of long-term drug use. The mechanism of action of mephedrone is associated with the stimulation of the structures of the mesolimbic system, and it acts by stimulation of dopaminergic, serotonergic and noradrenergic transmission. However, new data are still being published concerning its mechanism of action, thus, experiments searching for new targets for mephedrone are actual.

Metalloproteinases (MMPs) belong to the superfamily of multidomain zinc proteolytic enzymes, and are divided into 6 groups. Gelatinases, including MMP-9, have the most complicated MMP structure, and constitute the largest group of MMP in the CNS. Recent studies indicate the important role of MMP-9 in the development of the CNS, especially in the early period after birth (deemed "a critical time"). This comes about through its ability to control synaptogenesis, extend dendrites and axons, and induce myelination. Furthermore, MMPs can form a complex with TIMP-1. The major biological function of TIMP-1 is a fast inhibition of cell-released MMPs, especially MMP-9, that if not stopped soon enough may be detrimental to the tissues. Taking into account the now recognized increased expression and activity of MMP-9 in a number of pathological states (including neuropsychiatric disorders and addiction to psychoactive substances), its participation in the effects of mephedrone cannot be excluded.

In our proposed research project, we will assess the impact of mephedrone when administered to the male rats in adolescence, on the phenotypic changes in adults. In doing so, behavioral studies will be carried out to determine the effect upon adult behavior of such administration, while neurochemical studies will be undertaken to determine the role of matrix metalloproteinases (MMP-9) in the development of these changes. Pharmacological manipulation will be performed by adenovirally driven overexpression of TIMP-1 (adenoviral vector – AdRSVTimp1) into various brain structures (the NAc, prefrontal cortex, hippocampus) in order to verify/exclude the participation of MMP-9 in the development of these changes.

Implementation of this project will provide new information about the effects of mephedrone, one of the most commonly abused NPS. Should the project proceed, it will:

- 1) significantly expand existing knowledge about the mechanism of action of mephedrone, the short- and long-term effects of its abuse in adolescence and its importance in the development of various pathological states of the CNS in adults;
- 2) expand existing knowledge about the properties of MMP-9 and their role in the action of mephedrone;
- 3) be an interdisciplinary research project; it includes both behavioral and neurochemical experiments. Therefore, the project assumes at least a partial explanation of the mechanisms responsible for changes in animal behavior;
- 4) help to develop new strategies to combat the pathology resulting from the abuse of mephedrone;
- 5) be purely theoretical, however, the obtained results will be of extreme value for both the toxicological and the pharmacological sciences, and, as well for other fields of science, e.g. health care.

These studies will be conducted in several research centers (Lublin, Cracow) within Poland. The scientists involved in the project have been conducting research for many years, and have demonstrated expertise in these forms of research practices. Moreover, each of the assigned tasks is the dominant trend of research of each of the units participating in this project. Therefore, the aforementioned factors increase the chances of the successful implementation of the proposed research.