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Abstract of the PhD thesis entitled "**The effects of novel psychoactive substance, 25B-NBOMe on the central nervous system in comparison to psilocybin**"

After a half-century-long hiatus, studies concerning psychedelic drugs are relieving their renaissance. The breakthrough initiated with ketamine allowed other substances to be tested as a therapy for affective, anxiety, and addictive disorders, areas where classical treatment shows little effectiveness.

This dissertation aimed to characterize the effect of selective 5-HT2A agonist, 25B-NBOMe, on the central nervous system after acute and repeated administration. The next step was to compare it with the effects of a more promiscuous drug, psilocybin, with the use of a prototypical fast-acting antidepressant drug, ketamine, as a reference substance. To accomplish these goals, microdialysis in freely moving animals was performed to assess the extracellular levels of selected neurotransmitters; a battery of behavioral tests to evaluate locomotor activity, anxiety levels, and behavioral despair; molecular and histological techniques to investigate potential damage to the brain tissue and expression of chosen genes.

The gathered data shows a significant effect of 25B-NBOMe on glutamatergic, dopaminergic, serotonergic, and cholinergic neurotransmission in the frontal cortex, striatum, and nucleus accumbens. The increases in extracellular levels of studied neurotransmitters were not dose-dependent and exhibited a hormetic response. This is most likely a result of the stimulation of the 5-HT2A receptor and subsequent activation of the 5-HT2C receptor as the plasma levels of the drug increase. This effect was also observed in the wet dog shake (WDS) test, used to assess the hallucinogenic potential of the investigated compound, and also in the

locomotor activity measured in the open field test.

The next step was to evaluate the effects of chronic administration of 25B-NBOMe on the CNS. A rapid growth of tolerance, starting from the second day of treatment, was observed in the WDS test. The increases in extracellular levels of neurotransmitters were nearly all attenuated by the seventh day of treatment. What is interesting is that the increased levels of monoamines were still observed in the nucleus accumbens, suggesting the addictive properties of 25B-NBOMe. What is more, the chronic treatment with 25B-NBOMe leads to genotoxicity in the cortex and hippocampus and activation of microglia.

The next study investigated the effects of acute treatment with psilocybin on the dopaminergic, serotonergic, glutamatergic, and GABAergic transmission in the rat frontal cortex in comparison to a reference drug – ketamine. Psilocybin affected mainly the investigated amino-acidic neurotransmitters, while ketamine exerted a more robust effect on the monoamines. What is more, we have proven the hypothesized effect of psilocybin on cortico-thalamic gating, as psilocybin dose-dependently increased the release of GABA in the reticular nucleus of the thalamus. No effects of studied drugs were observed in the forced swim test 24h after the administration, but this assay may not be suitable for testing rapid-acting antidepressant drugs.

The last study investigated the influence of psilocybin and ketamine on the limbic neurotransmission. Significant changes were observed in extracellular levels of neurotransmitters in the nucleus accumbens and hippocampus but not in the amygdala. Psilocybin exhibited anxiolytic properties both 1 and 24h after its administration, which suggests a lasting anxiolytic effect. This may be a result of the observed intensification of GABAergic neurotransmission.

In summary, the gathered data indicates that selective 5-HT2A agonist 25B-NBOMe exerts a significant effect on rats' neurotransmission and behavior while also inducing oxidative DNA damage. The effects induced by psilocybin are more subtle, suggesting a broader therapeutic index of this drug. This is most likely due to its wider receptor profile and possible modulation via the 5-HT1A receptor.