ABSTRACT

Introduction: Since the beginning of this century, new synthetic drugs (NSD) have become a popular component of Czech Republic and worldwide drug scene. The main reason for their popularity and prevalence is their legality and the interest of users to seek new experiences. This leads to a constant production of substances with various chemical structure's modifications, but information about acute and chronic effects, pharmacology and toxicology are mostly missing or they are not sufficient.

Aims: The main aim of this doctoral thesis was to evaluate NSD from the ranks of cathinones. The subobjectives were as follows: 1) evaluation of stimulation potential 2) evaluation of potency to disrupt sensorimotor gating 3) evaluation of acute toxicity in terms of the risk of hyperthermia 4) evaluation of addictive potential.

Methods: The NSDs tested in this thesis were mephedrone (2.5, 5, 20 mg/kg), methylone 5, 10, 20, 40 mg/kg) and naphyrone (5, 10, 20 mg/kg). All NSDs were administered subcutaneously in a volume of 2 ml/kg. Adult male Wistar rats were behaviourally tested in the open field test (n = 10/group), the prepulse inhibition test (n = 10/group) and the conditioned place preference test (n = 13/group). For pharmacokinetic experiments, serum and organs (brain, lungs, liver) were collected at predetermined intervals, n = 8/group. To evaluate the effect of NSD on body temperature, the rectal temperature was measured, n = 10/group. The target structure for the microdialysis experiment was *nucleus accumbens* (NAcc) and dopamine levels were evaluated after NSD administration, n = 10/group.

Results: The investigated synthetic cathinones showed rapid absorption, fast crossing of blood-brain barrier and accumulation in lung tissue. Levels of synthetic cathinones in the brain were much higher than those in serum - the brain/serum ratio was 1.19 for mephedrone, 4.54 for methylone and 6.5 for naphyrone. The stimulation effect was present at all administered

substances with the most pronounced effect 5 min (mephedrone) and 15 min (methylone, naphyrone) after administration. Prepulse inhibition was not disrupted by any mephedrone or methylone dose, surprisingly we observed an improvement after naphyrone (20 mg/kg). All studied substances significantly increased the body temperature of rats regardless of housing conditions (alone vs. five). In the conditioned place preference test, naphyrone led to significantly increased preferential score for the arena associated with its administration. The lethal dose of methylone was 40 mg/kg.

Conclusion: Synthetic cathinones mephedrone, methylone and naphyrone had a stimulation effect, with mephedrone as the most potent stimulant. All substances induced hyperthermia, but compared to other serotonergic NSDs, their effect on body temperature was less robust. Thus, hyperthermia was most probably caused by increased behavioural activity rather than by a serotonin toxicity. Based on our findings, we evaluate mephedrone, methylone and naphyrone as substances acting mainly through dopaminergic neurotransmission with an addictive potential.