

### **Description for general public**

Addictions are a serious problem that cause the destruction of professional, social and family ties and increase delinquency, thus also endangering the wellbeing of the 'healthy' part of society. Despite extensive and long-term studies, an effective therapy for addiction remains beyond our reach. We still do not know the answer to the key question of why only a relatively small percentage of drug-using individuals become addicted, whereas others may continue drug abuse for many years with no grave consequences. Recognition of the diversified susceptibility to addiction and its key importance for the interpretation of the results of relevant studies has resulted in major changes in the methodology used in basic research on addiction. For instance, to discriminate between animals that control their use of addictive drugs and those that have switched to compulsive drug intake (the equivalents of recreational drug intake and addiction in humans), researchers have started to use criteria analogous to those used in the corresponding human clinical situations. This approach has enabled better modeling of addictions and study of differences between the biological effects observed in addiction-resistant individuals (transient changes in emotional state(s) that disappear due to active neuroadaptational processes that allow control to be maintained) and in addiction-prone individuals (permanent aberrations that result in the loss of control, compulsive drug use and the destruction of many facets of life). This is of critical importance because identification of differences between resistant and susceptible individuals brings us closer to understanding which of the addictive drug-induced changes determine the emergence of addiction.

**Rationale of the undertaken studies:** The main challenge in studies of addiction is the elucidation of why only a small fraction of drug (ab)users become addicted, whereas the great majority remains resistant. The two principal questions are the factors that determine the susceptibility to addiction and the differences in the biological effects of psychoactive substances between addiction-prone and -resistant individuals. The answer for the first one must be sought in not yet addicted individuals, i.e., those whose brains have not yet been permanently altered by drug (ab)use. For this, one needs the ability to predict susceptibility to addiction. Our recent studies revealed that rats that showed poor sensitization of their amphetamine-induced frequency-modulated 50-kHz ultrasonic vocalization response (FM 50-kHz USV, which is used by rodents for communication with their kin and is considered the best index of rat affective states, similar to self-report in humans) were much more likely to self-administer the drug than their highly sensitized counterparts. This observation suggests that this subset includes addiction-prone rats. The observed inter-individual diversification and intra-individual stability of this characteristic creates the hope that it may be a predictor of susceptibility to addiction. The answer to the second of the questions listed above will be sought by comparing the biological reactions of individuals who did or did not become addicted after long-term amphetamine self-administration.

**Objectives of the project:** (i) to verify the utility of a predictor based on sensitization of the FM 50-kHz USV response in rats subjected to the formation of addiction and assess whether this predictor has a genetic background; (ii) to search for neurobiological differences based on the expression of protein markers of neuroplasticity and release of selected neurotransmitters between amphetamine-addicted and amphetamine addiction-resistant rats; and (iii) to analyze changes in the FM 50-kHz USV response that take place during long-term amphetamine self-administration while considering individual susceptibility to the development of addiction.

**Planned investigations:** (i) categorization of the subject rats according to the amphetamine-induced sensitization of their FM 50-kHz USV response to amphetamine; (ii) verification of the utility of sensitization-based predictions of susceptibility to addiction based on the assessment of addiction after 70 amphetamine self-administration sessions; (iii) measurement and analysis of the FM 50-kHz USV response during the course of amphetamine self-administration and after completion of the course while taking into account differences in susceptibility to amphetamine addiction; (iv) HPLC-based determination of selected neurotransmitters in microdialysate samples and determination of the protein biomarkers (FosB, BDNF) expression in samples of selected brain regions after the completion of amphetamine self-administration; and (v) selective breeding (5 generations) of the rats that show poor and strong sensitization of the FM 50-kHz USV response to amphetamine and assessment of the final effect based on the addiction formed in the 5th generation by long-term amphetamine self-administration.