Abuse of methamphetamine and related compounds (amphetamine and ecstasy) presents a social and health challenge worldwide. Synthesis of these compounds is relatively easy from commonly available ingredients, with frequently media reports on “house laboratories” located in different parts of the country. For example, methamphetamine can be manufactured from pseudoephedrine, which is a component of several over-the-counter medications. Therefore, methamphetamine is less expensive than other drugs and thus favored by young people. It has strong psychostimulatory effects and high dependency potential. Methamphetamine is being used by approximately 35 million people worldwide.

In addition to its psychostimulatory impact, methamphetamine has also substantial neuro- and vascular toxicity. The long term effects of methamphetamine abuse are psychotic disorders, Parkinson’s disease, anxiety, and cognitive dysfunction. Importantly, methamphetamine stimulates disruption of the blood-brain barrier, which separates the brain tissue from factors present in the blood. An acute methamphetamine poisoning induces brain edema as a result of the disruption of this barrier.

Recent scientific advances have changed an old belief that a person is born with a specific number of neurons in the brain. It was assumed that this number can decrease due to neuronal death (for example, in response to exposure to toxic substances) but no new neurons are produced in an adult person. These concepts were changed dramatically with the discovery of neuronal stem cells (also called neuronal progenitor cells), which produce neurons throughout life, even in adult people. New neurons are formed in specific brain regions, one of which is the hippocampus. These new neurons are then incorporated into the existing neuronal networks. The whole process is critically important and enables normal memory and cognitive functions. Indeed, aberrant differentiation of neuronal progenitor cells into neuronal cells is linked to alterations of memory and cognition.

It is frequently overlooked that progenitor cells are located in close proximity to brain capillaries, which form the blood-brain barrier, separating and protecting the brain from blood-borne toxic factors. However, administration of methamphetamine disrupts this barrier. **The present application is built on these discoveries and focuses on the hypothesis that methamphetamine-induced dysfunction of the blood-brain barrier alters differentiation of neuronal progenitor cells into new neurons.**

The proposed experiments on the mechanisms of methamphetamine-induced disruption of the blood-brain barrier, and subsequent alterations of the generative process of new neurons, will be completed by studying the repair processes. This is an important approach as currently there are no widely accepted or effective methods to treat dependency and/or protect against relapses in methamphetamine abuse. However, aerobic exercise is being introduced as an adjuvant approach to treat various forms of addictions. Our published results indicate that exercise also improves the function of the blood-brain barrier. Therefore, **the second hypothesis tested in this proposal is the notion that exercise, by protecting against a disruption in the blood-brain barrier, enhances the formation of neurons from progenitor cells**.

This grant application is based on animal experimentation and will implement a model of voluntary aerobic exercise in mice on running wheels which are linked to a computer system. This allows the monitoring of the distance run by individual animals. Mice will be administered with methamphetamine in increasing doses, which mimics the pattern of drug intake by addicted people. The experiments will include the assessment of blood-brain barrier integrity and the expression of structural elements which determine this integrity. Differentiation of progenitor cells into neurons will be analyzed by molecular methods and visualization after staining for specific cell markers.

We predict that physical exercise will protect against methamphetamine-induced disruption of the blood-brain barrier and will have a positive impact on the differentiation of progenitor cells into neurons. These results will be applicable not only to methamphetamine toxicity but also other illicit drugs which affect the vascular system in the brain. We expect that the proposed studies will indicate that exercise can protect against drug toxicity and will contribute to more common use of behavioral therapies based on exercise in addiction treatment.