

Each minute 1 person around the world commits suicide due to depression. The disease is a leading cause of the global burden of disability and carries a persistent risk of relapse even during remission. Recently the scientists proved that the memory deficits co-occur with depression. Cognitive deficits not only impact the quality of life negatively but might also be the reason why antidepressant treatment is ineffective in around 60% percent of patients. Currently available antidepressants are inadequate, as they fail to improve memory impairments, have delayed onset of action, limited clinical effectiveness, and many side effects. Thus, our objective is to find a rapid-acting antidepressant that also improves cognitive function.

Based on our recent studies, we have selected HBK-15, a compound which showed rapid antidepressant-like effect and improved cognition in rodents. HBK-15 targets several receptors and channels, but its molecular and cellular mechanisms remain unknown. Thus, in this project, we aim to thoroughly investigate the positive effect of HBK-15 on learning and memory processes and find a cellular mechanism responsible for its rapid antidepressant-like and procognitive effect.

In the first year, we will synthesize HBK-15 in the amount necessary for our project and investigate whether HBK-15 targets more receptors/transporters/channels than the ones we have already tested. We will also assess the duration of antidepressant-like and memory-enhancing effects after a single administration of HBK-15 and begin investigating the influence of the compound on learning processes, as well as various types of memory. To achieve this, we will use multiple animal tests and models.

In the second year, we will focus on assessing antidepressant-like and procognitive properties of HBK-15 using more sophisticated, transitional animal models, which resemble tests used in humans. We will also start investigating the compound's cellular mechanism of action using various techniques, which help to label the proteins of interest and determine gene expression.

So far, the pharmacological activity of HBK-15 has been evaluated in male rodents. Research suggests, however, that brain regions responsible for mood and memory processes differ between sexes. Therefore, sex matters much more than has been widely assumed for understanding the effects of the drugs. Moreover, depression is more common in women than in men. Taking the above into account in the third year, we will begin evaluating the effect of HBK-15 in female mice.

As the outcome of the project, we expect to unravel HBK-15 mechanism of action and use this knowledge as the basis for the future development of rapid-acting antidepressants improving cognition.