

Information for research project

<i>Call:</i> Competition for financial support of basic research projects – 2022
<i>Main scientific area:</i> Biological Sciences
<i>Contract No:</i> КП-06 ПН61/9 от 2022 г./ BG-175467353-2022-04-0069 Type 2
<i>Initial date and duration of the project:</i> 30/11/2022; 36 (thirty six) months
<i>Project title:</i> Investigation of the role of neurogenesis in the modulatory influence of noradrenergic-mediated hippocampal consolidation in physiological and pathological conditions: New therapeutic approaches
<i>Research organization:</i> Institute of Neurobiology, Bulgarian Academy of Sciences
<i>Partner organizations:</i> Faculty of Medicine, Trakia University - Stara Zagora
<i>Principle investigator:</i> Assoc. Prof. Dimitrinka Yordanova Atanasova-Dimitrova, PhD

Abstract of the research project

Emotional arousal and **acute stress** favor the neurobiological processes associated with forming stable and lasting memories of the preceding events. Simultaneous activation of the noradrenergic and glucocorticoid systems modulates formation and long-term memory storage (**cellular consolidation**). Acute stress, as a result of unexpected changes in the environmental or social environment, is characterized by an adaptive response to the short-term increased secretion of cortisol in humans (corticosterone in rodents). In contrast, **chronic stress** induces systemically increased levels of plasma glucocorticoid hormone. This condition determines characteristic pathogenesis in brain structures associated with the formation of memory traces and abnormal behavioral responses known as allostatic overload. Even though the studies in this direction have been very intensive in recent years, the mechanisms regulating the emotional aspects of memory under different conditions are not fully understood. For this reason, the in-depth study of interactions between biological processes and environmental factors is necessary to determine the opposite effect on episodic memory exerted by **acute stress**, on the one hand, and **traumatic** and **chronic stress**, leading to affective and anxiety disorders on the other hand.

The current project **aims** to elucidate the role of neurogenesis in the hippocampal consolidation process, regulated by the noradrenergic and glucocorticoid systems under acute and chronic stress conditions, respectively. Fundamental research on this topic is necessary as a contextual framework for introducing new pharmacological approaches to alleviate the pathogenesis of affective states, including cognitive disorders. Agomelatine is a new generation antidepressant used in clinical practice in Europe. The drug possesses chronotropic activity due to its mechanism of action as a receptor MT₁ and MT₂ agonist and 5-HT_{2C} antagonist. Literature and our previous studies showed its positive influence on the three stages of neurogenesis in pathologies of different types. This data gives us the basis to formulate a **working hypothesis** that this melatonin analogue corrects cognitive disorders and the accompanying chronic stress overgeneralization caused by an abnormal behavioral response to situations with an emotionally neutral context. Knowing the mechanism underlying agomelatine therapeutic effects on cognitive deficits in chronic stress would contribute to developing new psychopharmacological agents that target cognitive deficits in affective and anxiety disorders.

The results of the current project is expected to have *fundamental significance*, which will help to acquire new knowledge related to the clarification of the role of neurogenesis in the process of modulation of consolidation in the hippocampus with the participation of noradrenergic neuromodulation and its interaction with the glucocorticoid system. Furthermore, deepening our knowledge of the molecular mechanisms involved in the processes of memory trace formation in acute and chronic stress would also have *translational* significance for developing more specific, innovative therapeutic strategies.

Teams composed of participants from various institutions, including the applying organization, the Institute of Neurobiology at the Bulgarian Academy of Sciences, and the partner organization, the Faculty of Medicine at Trakia University - Stara Zagora will use and apply specific approaches and methods to solve particular scientific tasks in various aspects.

Keywords: acute and chronic stress, neurogenesis, consolidation, emotional memory, cognitive deficit, norepinephrine, cortisol