**Naslov/Title:** Translacioni put za rasvetljavanje efekata tretmana agonistom GLP-1 receptora na funkciju osovine masno tkivo - mozak u kognitivnim procesima kod dijabetesa tipa 2 sa pridruženom gojaznošću

Translational road to elucidate the effects of GLP-1 receptor agonist treatment on adipose tissue - brain axis function in cognitive processes in diabetes type 2 with concomitant obesity

**Akronim/Acronym:** CoD-GOAT

**Rukovodilac projekta/Principal investigator (PI):** dr Jovana Aranđelović, naučni saradnik/research associate (Katedra za farmakologiju/Department of Pharmacology)

**Logo:**



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**Multidisciplinarni pristup projekta/ Multidisciplinary approach of the CoD-GOAT:**



**Projektni tim/CoD-GOAT team:**

|  |  |  |
| --- | --- | --- |
| Uloga na projektu/Project role | Ime i prezime istraživača I titula/ Researcher’s name and title | NIO/SRO |
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**Apstrakt/ Abstract:**

Diabetes mellitus type 2 (T2D) is associated with risk of dementia development, and more than half of T2D patients are obese. However, antidiabetic drugs, glucagon-like peptide-1 receptor (GLP-1R) agonists, have been shown to be effective in treating T2D with concomitant obesity (T2D+O) and may reduce risk of dementia development. GLP-1R agonists act both centrally and peripherally, but their mechanism of action on cognitive impairment in T2D+O is poorly understood. However, several evidence suggested that GLP-1R activation in the hippocampus promotes GABAergic transmission. In addition, GLP-1R agonists have been shown to affect adipokine levels. Alterations in adipokine signalling also underlie cognitive impairment in T2D+O. Therefore, our goal is to unravel the molecular changes induced by GLP-1R agonists that are associated with alleviation of cognitive impairment and adipokine status in a preclinical model of T2D+O. To explore the translational potential of our findings, we will examine the effects of GLP-1R agonists on cognitive status and adipokine secretome in human patients with T2D+O before and after 6 months of therapy. In addition, we will evaluate for the first time the effects of a positive allosteric α5 GABAA receptor modulator (PAM) on cognitive impairment and adipokine profile in a preclinical T2D+O model. Cognitive status and adipokine levels in the T2D+O rat model and in human patients will be determined by cognitive tests and Luminex, respectively. The altered molecular pathways and genes in the hippocampus affected by GLP-1R agonist and PAM treatments in the preclinical model will be determined by bulk RNA sequencing analysis. Discovering the molecular mechanisms of selected treatments and adipokines associated with cognitive status, will accelerate drug repurposing, drug discovery, and the initiation of biomarker development in this field, which is of high importance since the efficacy of current therapies for cognitive impairment is limited.

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