

KOGNITIVNO OŠTEĆENJE I ANHEDONIJA KAO POTENCIJALNE KOMPLIKACIJE DIJABETESA TIP 2: PREKLINIČKA PERSPEKTIVA

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Dijabetes tipa 2 (T2D) predstavlja veoma često metaboličko oboljenje koje je snažno povezano sa nezdavim životnim navikama i gojaznošću. Ipak, hiperglikemija i poremećaj u signalizaciji insulina ne dovode samo do komplikacija u perifernim organima, već utiču i na funkciju mozga. T2D je jedan od glavnih faktora rizika za razvoj demencije, pri čemu su efekti potencijalno zavisni od pola. U skladu s tim, kognitivno oštećenje je u novijoj naučnoj literaturi sve više prepoznato kao nova komplikacija dijabetesa tipa 2 [1]. Pored toga, depresija se često javlja zajedno sa T2D zbog preklapanja faktora rizika, naročito onih povezanih sa životnim stilom i genetikom. Međutim, molekularni mehanizmi koji stoje u osnovi promena u mozgu izazvanih metaboličkim disbalansom u T2D i dalje su nedovoljno istraženi. Dodatno, antidijabetik semaglutid je u novijim studijama pokazao povezanost sa ublažavanjem kognitivnog oštećenja [2, 3] što ukazuje na njegov mogući efekat na modulaciju moždanih funkcija. U skladu s prethodno navedenim, cilj naše studije je bio da se istraži uticaj T2D na mozak putem bihejvioralne procene kod T2D modela pacova oba pola. Takođe, ispitali smo efekte terapije semaglutidom u ovom modelu. Zaista, kognitivna oštećenja i anhedonija su uočeni kod T2D model životinja u poređenju sa kontrolnim grupama, dok je semaglutid pokazao ohrabrujuće, polno-zavisne efekte na ove poremećaje. Zaključno, translaciono relevantan model T2D zajedno sa proširenom bihejvioralnom analizom može ponuditi opsežnije razumevanje uticaja ove bolesti i semaglutida na centralni nervni sistem, koje se dalje može povezati sa potencijalnim molekularnim promenama u moždanim strukturama uzrokovanim T2D.

Literatura

1. Sjöholm Å, Bennet L, Nilsson PM. Cognitive dysfunction in diabetes - the 'forgotten' diabetes complication: a narrative review. *Scand J Prim Health Care*. 2025;43(2):448-454.
2. Lin HT, Tsai YF, Liao PL, Wei JC. Neurodegeneration and Stroke After Semaglutide and Tirzepatide in Patients With Diabetes and Obesity. *JAMA Netw Open*. 2025;8(7):e2521016.
3. Tipa RO, Balan DG, Georgescu MT, Ignat LA, Vacaroiu IA, Georgescu DE, Raducu L, Mihai DA, Chipperi LV, Balcangiu-Stroescu AE. A Systematic Review of Semaglutide's Influence on Cognitive Function in Preclinical Animal Models and Cell-Line Studies. *Int J Mol Sci*. 2024;25(9):4972.

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COGNITIVE IMPAIRMENT AND ANHEDONIA AS POTENTIAL DIABETES TYPE 2 COMPLICATIONS: A PRECLINICAL PERSPECTIVE

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Diabetes type 2 (T2D) is a very common metabolic disorder strongly associated with poor lifestyle choices and obesity. However, hyperglycemia and impaired insulin signalling not only lead to complications in the periphery but also affect brain function. T2D is one of the main risk factors for the development of dementia, as it suggested, in a sex-dependent manner. In line with this, cognitive impairment has received attention as an emerging complication of T2D in recent scientific literature [1]. Similarly, depression may also co-occur with T2D due to overlapping lifestyle and genetic factors. However, the molecular mechanisms underlying brain changes caused by metabolic imbalance in T2D remain largely unexplored. Furthermore, the antidiabetic drug semaglutide has shown potential in treating cognitive impairment in recent studies [2, 3] suggesting an effect on brain modulation. Thus, we investigated how T2D affects the brain through behavioral testing in a rat T2D model of both sexes. In addition, we have evaluated the effects of semaglutide treatment in this model. Indeed, both cognitive impairment and anhedonia were observed in T2D animals compared to controls, while semaglutide showed promising sex-dependent effects on these conditions. In conclusion, the translationally relevant T2D model, combined with an extensive behavioral test battery, may offer a comprehensive understanding of the disease and the effects of semaglutide on the central nervous system, which could be further linked to potential molecular changes in brain structures caused by T2D.

References

1. Sjöholm Å, Bennet L, Nilsson PM. Cognitive dysfunction in diabetes - the 'forgotten' diabetes complication: a narrative review. *Scand J Prim Health Care*. 2025;43(2):448-454.
2. Lin HT, Tsai YF, Liao PL, Wei JC. Neurodegeneration and Stroke After Semaglutide and Tirzepatide in Patients With Diabetes and Obesity. *JAMA Netw Open*. 2025;8(7):e2521016.
3. Tipa RO, Balan DG, Georgescu MT, Ignat LA, Vacaroiu IA, Georgescu DE, Raducu L, Mihai DA, Chipari LV, Balcangiu-Stroescu AE. A Systematic Review of Semaglutide's Influence on Cognitive Function in Preclinical Animal Models and Cell-Line Studies. *Int J Mol Sci*. 2024;25(9):4972.

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