Cellular and Molecular Neurobiology (2025) 45:22
https://doi.org/10.1007/s10571-025-01534-4

ORIGINAL RESEARCH

Beyond Diabetes: Semaglutide's Role in Modulating Mood Disorders through Neuroinflammation Pathways

Iwona Piątkowska-Chmiel[1] · Katarzyna Wicha-Komsta[2] · Kamil Pawłowski[1] · Aleksandra Syrytczyk[1] · Tomasz Kocki[2] · Jarosław Dudka[1] · Mariola Herbet[1]

Received: 10 September 2024 / Accepted: 25 January 2025

Abstract
Diabetes and mood disorders are intricately interconnected, with each condition elevating the risk of the other. This bidirectional relationship, further exacerbated by neuroinflammation, fosters an environment conducive to the development of anxiety and depression. Glucagon-like peptide-1 receptor agonists, such as semaglutide, offer promising therapeutic options that not only target type 2 diabetes but also can positively influence mood. Our study's primary goal was to evaluate the effectiveness of semaglutide, in mitigating anxiety and depression within an animal model of diabetes. The neuroprotective properties of semaglutide were evaluated by examining its influence on the kynurenine pathway and neurobiological markers (GFAP, NEFL, NSE, and GAL3) in the perfrontal cortex, selected for its key role in cognitive function and emotional regulation, impaired in diabetes and mood disorders. Additionally, we examined semaglutide's impact on peripheral inflammation and stress parameters to elucidate its role in modulating systemic inflammatory responses linked to mood disorders. Additionally, we conducted behavioral assessments to better understand how semaglutide influences anxiety and depression-related behaviors in diabetic mice. Semaglutide therapy significantly improved behavioral patterns and neurochemical markers in diabetic mice. The frequency of administration significantly influenced the outcomes, whereas the dosage appeared to have a limited impact. Here we show that semaglutide expands its therapeutic potential beyond diabetes, significantly influencing mood disorders through neuroinflammatory pathways. Semaglutide has the potential to be a key element in formulating integrated treatment strategies that address both metabolic health and mental well-being, ultimately enhancing the quality of life for individuals navigating these interrelated challenges.

Keywords Diabetes · Semaglutide · Mood disorders · Neuroinflammation · Anxiety · Depression

Introduction

The connection between diabetes and mental health is becoming increasingly apparent. Managing a chronic condition like diabetes can be emotionally overwhelming, as daily responsibilities such as blood sugar monitoring, dietary restrictions, and medication adherence often lead to stress, anxiety, and frustration (Semenkovich et al. 2015). Anxiety can heighten concerns about diabetes control, causing hypervigilance or even avoidance of essential tasks, which in turn disrupts glycemic management. Depression further complicates this by reducing motivation for self-care, making it harder to follow dietary plans or medication routines (Steel et al. 1987; Bădescu et al. 2016). Additionally, eating pattern disruptions, which are more prevalent among diabetic patients, can exacerbate both anxiety and mood disorders (Bădescu et al. 2016; Milaneschi et al. 2019; Dziewa et al. 2023). This creates a vicious cycle, where the overlapping symptoms of diabetes and mental health conditions, such as fatigue or changes in appetite, blur the lines between the two, complicating treatment and contributing to further psychological and physical health decline.

The relationship between diabetes and mental health is not solely due to psychological factors; it has biological underpinnings. It is believed that oxidative stress (cell

✉ Iwona Piątkowska-Chmiel
iwona.piatkowska-chmiel@umlub.pl

[1] Department of Toxicology, Faculty of Pharmacy, Medical University of Lublin, 8B Jaczewskiego Street, 20-090 Lublin, Poland

[2] Department of Experimental and Clinical Pharmacology, Faculty of Medicine, Medical University of Lublin, Lublin, Poland

Published online: 10 March 2025

damage caused by free radicals), chronic neuroinflammatory processes, disruptions in neurogenesis and synaptogenesis, as well as an imbalance in the level of neurotransmitters play a key role in the pathology of anxiety and depressive disorders (Gold et al. 1988; Zunszain et al. 2011; Malhi and Mann 2018). Considering that glucose is a key compound for the proper functioning of neurons, metabolic disorders in the course of diabetes may also play a significant role in depression (Głombik et al. 2020; Detka et al. 2015). Research has shown that both diabetes and mental illnesses like anxiety disorders and major depression are associated with changes in brain regions involved in emotional regulation and stress response. Patients with depression exhibit impaired neuronal activity and disrupted synaptic plasticity, leading to structural alterations in brain regions involved in emotion and stress regulation, such as the hippocampus and prefrontal cortex. The areas of the brain that may be affected by these changes are the amygdala (involved in processing emotions and fear), the prefrontal cortex (involved in decision-making and emotional regulation), and the hippocampus (involved in memory and stress response) (Liu et al. 2017).

Increased degradation of tryptophan towards kynurenine (KYN) and shift away from serotonin production have been associated with several psychiatric diseases, including depression (Kegel et al. 2014; Réus et al. 2015; Myint et al. 2012). Available test results have revealed that stress and the activation of pro-inflammatory cytokines noted in depression can increase the activity of indoleamine 2,3-dioxygenase (IDO) in the peripheral tissues and the brain, leading to increased degradation of tryptophan and towards synthesis of detrimental tryptophan catabolites (TRYCATs) (Maes et al. 2011). IDO activity is negatively correlated with serotonin levels (Qin et al. 2018; Quak et al. 2014; Maes et al. 2011), which has been proposed as a common mechanism linking depression and diabetes (de Silva Dias et al. 2016). Supporting this notion, De Silva et al. observed a significant increase in pro-inflammatory cytokines alongside a decrease in serotonin levels in diabetic rats, suggesting that IDO activation may contribute to depressive-like behaviors. Moreover, it was noticed that individuals grappling with fatigue and depression display a perturbed equilibrium between neuroprotective and neurodegenerative tryptophan degradation metabolites (Savitz et al. 2015; Myint et al. 2012). Studies on rodents have shown that compounds modulating the KYN pathway have antidepressant effects (Zhu et al. 2015; Ara and Bano 2012). Interestingly, among the compounds that were able to reverse changes in the KYN pathway were some SSRI (selective serotonin reuptake inhibitor) antidepressants (Ara and Bano 2012; Franklin et al. 2012). Therefore, compounds that are involved in the KYN pathway may play a key role in both the pathogenesis and treatment of mood disorders.

Given the limited efficacy of current antidepressants, there is an increasing need to explore alternative approaches that more effectively address the intricate relationship between anxiety, depression, and diabetes. Although GLP-1 analogs are primarily utilized for glucose regulation and appetite control, emerging evidence suggests their significant role in central nervous system (CNS) disorders (Katsurada and Yada 2016). GLP-1 receptor (GLP-1R) signaling has been shown to protect neurons, enhance synaptic function, promote neurogenesis, and reduce oxidative stress and apoptosis (Duarte et al. 2020; McClean et al. 2015; Batista et al. 2019). These neuroprotective effects have led to the investigation of GLP-1R agonists in neurodegenerative diseases such as Alzheimer's and Parkinson's (Duarte et al. 2020). Additionally, growing evidence highlights their potential in treating neuropsychiatric conditions, including depression (Kim et al. 2020; Anderberg et al. 2016). Preclinical studies and clinical trials have demonstrated that GLP-1R agonists may produce antidepressant effects by modulating neuroinflammatory pathways (Velmurugan et al. 2012; Ventorp et al. 2017). Dudek et al. (2020) further propose that GLP-1R agonists can protect the blood–brain barrier from inflammation-induced damage, which is commonly observed in individuals suffering from both diabetes and depression (Zunszain et al. 2013; Piatkowska-Chmiel et al. 2021).

Recent findings from studies involving both humans and animals suggest that GLP-1R agonists may play a key role in regulating stress responses and anxiety-related behaviors by affecting the hypothalamic–pituitary–adrenal (HPA) axis (Gil-Lozano et al. 2010; Winzeler et al. 2019; Holt and Trapp 2016; Kim et al. 2020). However, it's important to note that the data collected thus far are inconclusive, and further research is needed to establish a clearer understanding of this relationship. Apart from that, GLP-1Rs may directly affect neurotransmitter activity, which could contribute to improvements in mood and emotional well-being.

GLP-1R signaling is crucial for maintaining mitochondrial integrity in hypothalamic astrocytes (Timper et al. 2020). A postmortem study found reduced GLP-1R expression in the dorsolateral prefrontal cortex and hippocampus of individuals with mood disorders (Mansur et al. 2018). In a chronic corticosterone-induced depression mouse model, liraglutide reduced depressive and anxious behaviors, mitigated corticosterone-induced hyperactivity, and preserved synaptic plasticity, unlike fluoxetine, which failed to alleviate hippocampal long-term potentiation suppression (Weina et al. 2018). GLP-1R agonists may serve as adjunctive therapies for cognitive impairments related to depression, particularly in women, as evidenced by exendin-4 enhancing cognitive performance in female mice (Trammell et al. 2021). Additionally, GLP-1R antagonists have been linked to significant increases in serotonin levels and metabolites, potentially impacting depressive disorders (Owji et al.

2002). Inflammation associated with diabetes and depression can activate the kynurenine pathway, reducing tryptophan availability for serotonin synthesis (Qin et al. 2018). GLP-1 analogs with anti-inflammatory properties may modulate this pathway, influencing the balance between neuroprotective and neurodegenerative metabolites, which is vital given the pathway's link to various neurological and psychiatric disorders, including depression.

The objective of our study was to elucidate the intricate relationships between metabolic dysfunction and mood regulation, emphasizing the potential of semaglutide as a promising intervention for mood disorders associated with diabetes. Recognizing the existing gaps in our understanding of semaglutide's impact on the kynurenine pathway—a critical biochemical pathway intertwined with both diabetes and neuropsychiatric complications—our research sought to provide new insights into this complex relationship. We also sought to assess the impact of semaglutide on key neurobiological markers such as GFAP, NEFL, NSE, and GAL3 within the brain perfrontal cortex, a region integral to emotional regulation and cognitive function, to provide a more detailed picture of its neuroprotective effects in the context of depression. Moreover, we examined levels of C-reactive protein (CRP) and magnesium in blood serum to further investigate semaglutide's influence on inflammation and stress, two critical factors that often exacerbate diabetes-related complications. By addressing both metabolic and neurobiological dimensions, we hoped to offer a comprehensive understanding of semaglutide's potential in mitigating the intertwined challenges of diabetes and mental health disorders.

Materials and Methods

This section presents a comprehensive overview of the methodologies employed in our study, aimed at rigorously examining the role of semaglutide in modulating anxiety and depression-like behaviors within a type 2 diabetes (T2D) mouse model.

Animals, Diet, and Drugs

Seven-week-old male CD-1 mice (The Experimental Medicine Centre (EMC) at the Medical University of Lublin, Poland) were housed in groups of four per cage under standard conditions, i.e., a constant temperature of 20–21 °C ± 1 °C, humidity at 60 ± 10%, with a 12-h light/dark cycle. Each experimental group consisted of eight animals randomly assigned.

The first group consisted of control mice (CTL) that had unrestricted access to standard feed diet and water throughout the experiment. The subsequent experimental groups II–VI included mice in which type 2 diabetes (T2D) was induced. This induction involved four weeks of access to a 20% aqueous fructose solution, followed by daily intraperitoneal injections of freshly prepared streptozotocin (STZ) solution (at a dosage of 40 mg/kg body weight for five consecutive days. This model was designed and comprehensively described in our prior publication (Piatkowska-Chmiel et al. 2021).

In the next stage, semaglutide (Ozempic, Novo Nordisk, Bagsværd, Denmark) was administered to mice with confirmed type 2 diabetes (T2D), i.e., with a blood glucose level ≥ 200 mg/dl. Semaglutide was administered subcutaneously (sc) once a week for two weeks to groups III and V. The dose used for group III was 0.21 mg/kg and for group V was 0.42 mg/kg. Semaglutide in groups IV and VI was administered once daily for two weeks in doses of 0.03 mg/kg or 0.06 mg/kg sc, respectively. In this study, a II group of animals with T2D did not undergo the drug administration procedure. In this phase of the experiment, animals in the control group (CTL) and the group with diabetes received equal volumes of physiologic saline (Scheme 1).

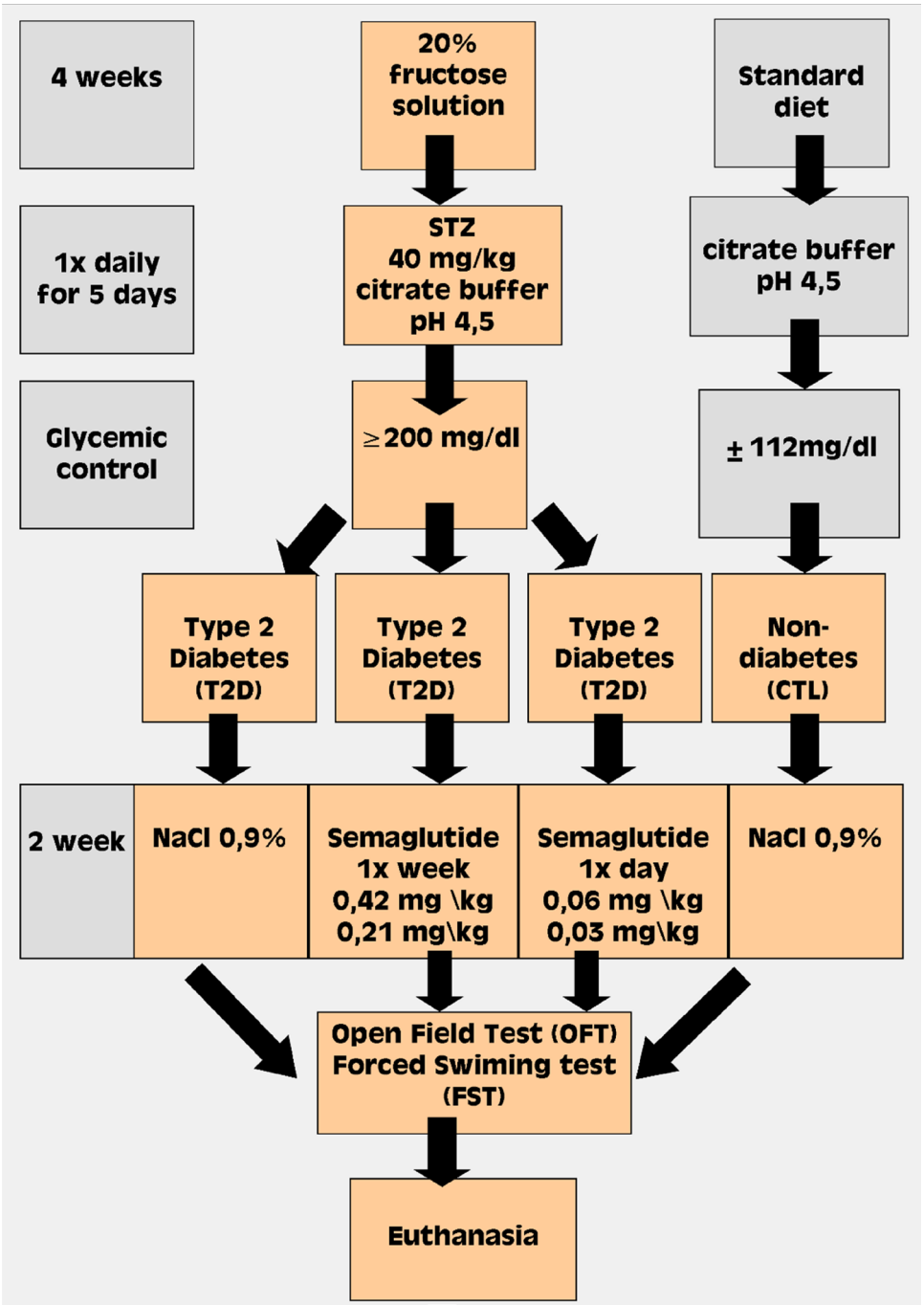
Animal care and experimental procedures adhered to the binding European standards for research on animal models (Act from January 15, 2015, on the Protection of Animals, Used for Scientific or Educational Purposes; Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes). These procedures received approval from the Local Ethics Committee at the University of Life Science in Lublin. The requirements of statistical analyses determined the total number of animals used, the Three Rs (3Rs), and the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments).

Behavioral Tests

Following the 2 weeks of administration of the drug or physiologic saline, the animals underwent a series of behavioral tests, starting with the least stressful paradigm and progressing to the most stressful one. An open field was used to examine anxiety-like behaviors and the forced swim test (FST) was used to evaluate depression-like behaviors. The behavioral tests were performed in a controlled environment from 9 a.m. to 2 p.m., in a separate room that was maintained at an appropriate temperature and intensity of light and noise. To ensure hygiene, the apparatuses were regularly disinfected between each animal. None of the mice had any previous contact with the tests performed.

Open Field Test (OFT)

The test followed the procedure outlined by Hall and Ballachey (1932), using a wooden box with dimensions of



Scheme 1. Mouse model of type 2 diabetes and drug administration: experimental design

40 × 40 cm for the floor and walls measuring 35 cm in height. Each mouse was placed individually in the center of the arena and allowed to explore freely for an uninterrupted period of 5 min. The anxiety level was assessed based on the animals' activity in the central arena, which is a highly anxiety-producing environment. To evaluate semaglutide's impact on anxiety-like behavior, the assessment was conducted 24 h after the final drug administration.

Forced Swimming Test (FST)

The Forced Swim Test (FST) was conducted following the method outlined by Porsolt et al. (1977), with minor adjustments aimed at improving the reliability of detecting potential antidepressant-like effects of the tested drug (Slattery and Cryan 2012). Glass tanks, measuring 25 cm in height and 10 cm in diameter, were utilized, filled with water maintained at a temperature between 23–25 °C, with a depth of

approximately 15 cm. Each mouse underwent individual placement in a tank for 6 min. The test session was recorded using a video camera and later analyzed by two investigators who were blinded to the experimental conditions. We quantified the immobility time (in seconds) of the mice during the final 4 min of the test. Immobility, defined as the absence of movement, except to maintain the head and nose above water, was regarded as an indicator of depressive behavior.

Neurochemical Analysis

One day following the behavioral tests, mice were killed by decapitation. On the day of decapitation, the brain from each animal was removed, and immediately the cortex was isolated to determine the levels of GFAP, NSE, NEFL, and GAL3.

Brain Samples Preparation and Quantitative Analysis of GFAP, NEFL, NSE, and GAL3

Briefly, after isolation, the tissues were rinsed in ice-cold PBS to remove excess blood thoroughly and weighed. Then, the tissues were homogenized in fresh lysis buffer (w:v = 1:50) on ice. The resulting suspension was sonicated with an ultrasonic cell disrupter till the clear solution. Next, homogenates were centrifuged at 10,000*g* for 5 min at 4 °C to obtain supernatants, which were stored at − 20 °C until use. Total protein concentrations for all homogenates were assayed using the Bradford method (Bradford 1976).

The concentrations of neurobiological markers in supernatants were assessed by enzyme-linked immunosorbent assay (ELISA Kits for mice: GFAP, NEFL, NSE, and GAL3; Cloud-Clone Corp., Houston, TX, USA). Each parameter was determined individually in all samples according to the manufacturer's protocols. The concentrations of neurobiological markers were determined by comparing the optical density of the samples to the standard curve. The limit of detection (LoD) was as follows: GFAP 6.3 pg/ml, NSE 29 pg/ml, NEFL 48.5.pg/ml, and GAL3 6.3 pg/ml. Neurobiological marker concentrations in the cortex were expressed in picograms per ml.

Brain Samples Preparation and Determination of KYNA, KYN, TRP

Samples of perftontal cortex were homogenized in water (1:9 w/v) and centrifuged at 14,000 rpm. The supernatant was acidified with 8% trichloroacetic acid (0.5 ml for each 100µL of supernatant). Samples were then vortexed, kept at 4º C for 20 min, and centrifuged again at 14,000 rpm.

Supernatants were analyzed by a high-performance liquid chromatography (HPLC) system (The UltiMate 3000 Analytical systems, Thermo Fisher Scientific, USA) according to Zhao et al. (2010). The mobile phase was composed of 20 mmol/l NaAc, 3 mmol/l ZnAc2, and 7% acetonitrile. It was pumped at a flow rate of 1 ml/min and the volume per injection was 100 µL, the analytical column was the Agilent HC-C18 (2); 250 × 4.6 mm i.d.; 5 m particle size. The wavelength of the UV detector was set to 365 nm (for L-KYN) and 250 nm (for TRP); KYNA was quantified fluorimetrically (excitation 344 nm with detection at 398 nm).

Biochemical Analysis

Blood samples were collected in tubes without anticoagulant and kept for at least 20 min to allow clot formation. Then the tubes were centrifuged at 4000 rpm for 10 min at 20 °C. This process enabled the separation of serum from morphotic elements, such as red and white blood cells and platelets, resulting in pure blood serum. The serum was then transferred to new tubes and immediately analyzed.

Serum Biomarker Analysis

The C-reactive protein (CRP) levels were assessed using the immunoturbidimetric method (BioMaxima, Lublin, Poland), while magnesium levels were quantitatively analyzed using a colorimetric method with a diagnostic kit (Wiener lab., Rosario, Argentina). The concentrations of CRP and magnesium were expressed in mg per dl, whereas corticosterone concentrations were expressed in mg per ml.

Statistical Analysis

The results were analyzed in two ways. First, a multi-way nested ANOVA was carried out, testing the following factors:

- Significance of diabetes (does diabetes change significantly the analyzed parameter).
- Significance of semaglutide nested in diabetes (does semaglutide significantly change the analyzed parameter in animals with type 2 diabetes).
- Significance of dose nested in semaglutide (are there significant differences between two doses of semaglutide).
- Significance of treatment regimen nested in semaglutide (are there significant differences between two regimens of treatment with semaglutide).

Additionally, for reference, one-way ANOVA done between all groups is depicted in Figures, together with multiple comparison tests by Student t-test with Bonferroni correction. Statistics were done in R Studio (R version 4.3.1) and visualized with the GGPlot2 package. The significance criterion was set at $P < 0.05$, denoted by an asterisk when

compared to the control group and a hashtag when compared to the T2D mice group.

Results

Semaglutide Mitigates Anxiety and Depressive-Like Behavior in Type 2 Diabetic Mice

The time spent by animals in the central zone of the field was significantly reduced in the diabetes mice group compared to the healthy animals ($F_{(1,43)} = 3.36$, $P < 0.1$) (Fig. 1A). Notably, fourteen days of semaglutide therapy exerted a significant effect on this measure compared to the diabetic animal group ($F_{(1,43)} = 7.81$, $P < 0.01$). Regarding dosage, it was not deemed a significant factor ($F_{(1,43)} = 0.597$, $P > 0.1$), while the frequency of drug administration to the afflicted mice emerged as notably significant ($F_{(1,43)} = 7.21$, $P < 0.05$). Importantly, the ANOVA results revealed no statistically significant differences in the number of crossings in the Open Field Test (OFT) between the control group and the diabetic mice (Fig. 1B). Furthermore, treatment with semaglutide did not produce significant effects on the number of crossings when compared to the untreated group of animals ($P > 0.05$). As shown in Fig. 1C, while diabetes led to a significant increase in the immobility time in the forced swim test (FST) compared to the healthy control group in multiple comparison tests, this difference did not reach significance in the ANOVA results, likely due to variations in variance ($F_{(1,43)} = 0.737$, $P > 0.1$). Notably, the reversal of the depressive effects of diabetes by semaglutide was statistically significant ($F_{(1,43)} = 10.7$, $P < 0.01$), with no significant differences observed based on the administered dose ($F_{(1,43)} = 0.0813$, $P > 0.1$), as well as on the frequency of administration of a drug ($F_{(1,43)} = 2.32$, $P > 0.1$). Daily administration for fourteen days showed slightly stronger effects, as evidenced by multiple comparison results—a significant difference was observed between the diabetic group (T2D) and both groups receiving daily drug administration throughout the treatment period (Fig. 1C).

Semaglutide Modulates Neurochemical Markers in Diabetic Mice Displaying Behavioral Patterns Similar to Anxiety or Depression: Analysis of GFAP, NSE, NEFL, and GAL3

A significantly lower level of GFAP was observed for animals with diabetes compared to control animals ($F_{(1,43)} = 58.9$, $P < 0.001$), however, semaglutide did not switch the level significantly back in treated animals ($F_{(1,43)} = 1.72$, $P > 0.1$) (Fig. 2A). Furthermore, among mice treated with semaglutide, no significant differences were observed in the level of this parameter across any of the treatment dosing amount ($F_{(1,43)} = 0.0922$, $P > 0.1$). Likewise, the variability between drug administration frequencies was deemed nonsignificant at the 95% confidence level ($F_{(1,43)} = 3.37$, $P < 0.1$). Diabetes increased the level of NSE, but the increase was not statistically significant ($F_{(1,43)} = 0.114$, $P > 0.1$) (Fig. 2B). However, the ANOVA test proved the overall lowering effect of semaglutide on the NSE level ($F_{(1,43)} = 25.4$, $P < 0.001$). Particularly noteworthy was the significant disparity observed between the diabetic group and both groups receiving the drug, once daily for 14 days, as indicated by significant findings in the ANOVA analysis ($F_{(1,43)} = 9.54$, $P < 0.01$). The frequency of drug administration (once a week or once a day for 2 weeks) significantly affects the NSE level in the cerebral cortex of treated mice compared to diabetic animals (ANOVA ($F_{(1,43)} = 9.54$, $P < 0.01$). However, the level of the tested parameter was not dependent on the dose of semaglutide used ($F_{(1,43)} = 0.384$, $P > 0.1$). Similar to NSE, diabetes increased the level of NEFL insignificantly ($F_{(1,43)} = 0.353$, $P > 0.1$). However, semaglutide decreased this level back to levels similar to the control group and the difference between non-treated and treated animals was significant in the ANOVA test ($F_{(1,43)} = 23.1$, $P < 0.001$). The dose of semaglutide is a significant factor because the lower dose gave significantly (at 90% level) lower NEFL level than the higher dose ($F_{(1,43)} = 2.86$, $P < 0.1$). No significant difference was observed between dosing regimens ($F_{(1,43)} = 0.0181$, $P > 0.1$).

In the case of the GAL3 parameter, a significant increase of its concentration was observed in the perfrontal cortex of diabetic animals compared to the healthy control group ($F_{(1,43)} = 9.47$, $P < 0.01$) (Fig. 2D). In multiple comparison tests, significance was observed only in changes in the tested parameter between the T2D group and the groups receiving the drug once daily for 14 days. Frequency of drug administration emerged as a significant factor in the ANOVA test ($F_{(1,43)} = 29.5$, $P < 0.001$). However, no significant difference was noted between the lower and higher doses of the drug ($F_{(1,43)} = 3.95$, $P < 0.1$).

Semaglutide's Role in Modulating the Kynurenine Pathway

It cannot be definitively concluded that there is a significant reduction in TRP levels in diabetes; the ANOVA significance only reaches a 90% level ($F_{(1,43)} = 3.03$, $P < 0.1$), and the multiple comparison test does not detect a significance (Fig. 3A). Similarly, the impact of semaglutide treatment on TRP levels is considered insignificant according to the ANOVA test ($F_{(1,43)} = 1.25$, $P > 0.1$). Diabetes did not also induce significant changes in KYNA levels ($F_{(1,43)} = 0.228$, $P > 0.1$), and likewise, semaglutide did not exert a significant impact on KYNA levels ($F_{(1,43)} = 1.95$, $P > 0.1$) (Fig. 3B). While the ANOVA underscores the significance of semaglutide dosage

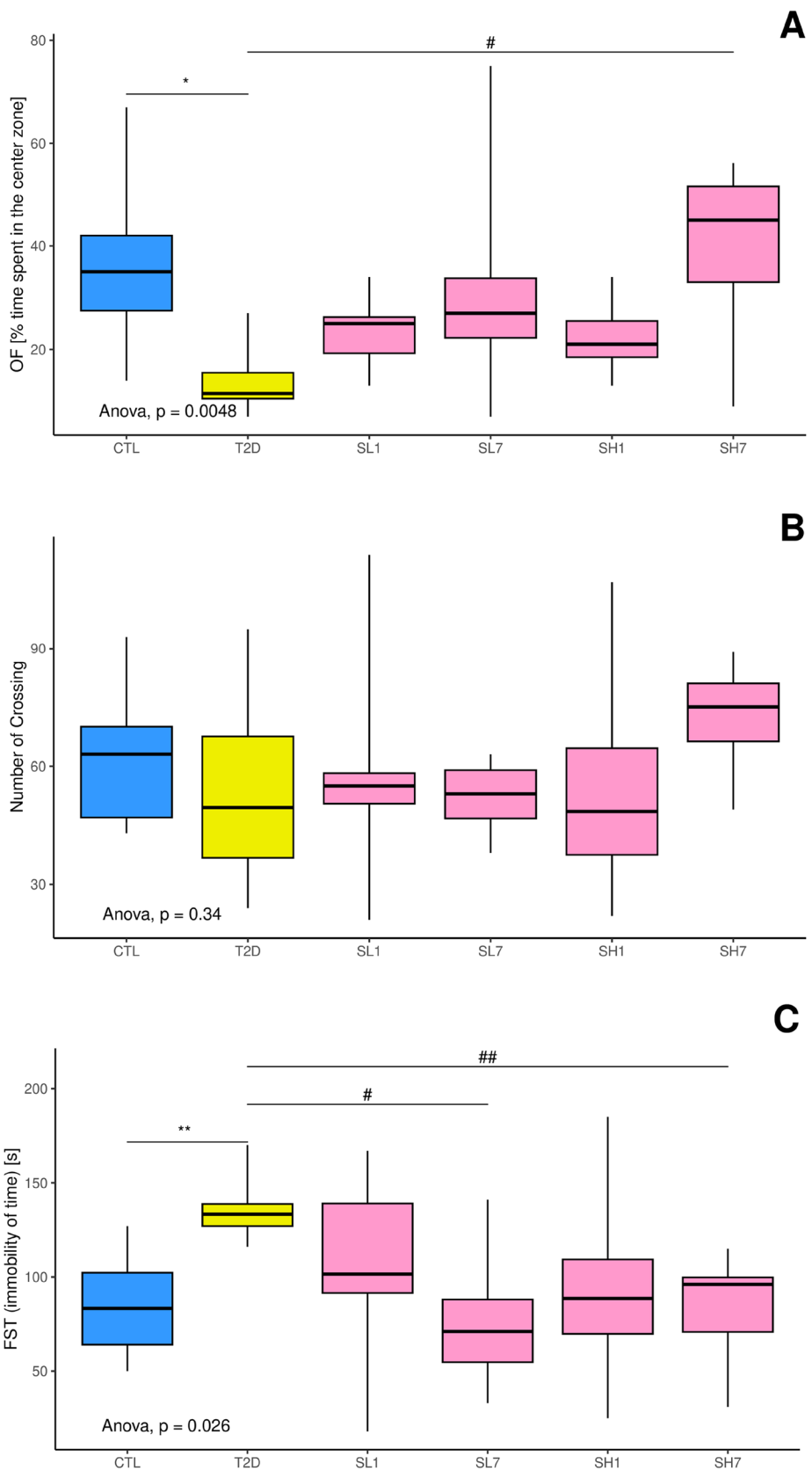


Fig. 1 Semaglutide's effects on anxiety- and depression-like behaviors in T2D mice. **A**, **B** Open Filed (OF); **C** Forced Swimming Test (FST). CTL: control mice, T2D: mice with diabetes; SL1: diabetic animals receiving a lower dose of semaglutide once weekly; SL7: diabetic animals receiving a lower dose of semaglutide once daily for 14 days; SH1: diabetic animals receiving high dose semaglutide once weekly; SH7: diabetic mice receiving a higher dose of semaglutide once daily for 14 days. The statistical analysis employed one-way ANOVA in conjunction with multiple comparison tests using the Student t-test with Bonferroni correction. A significance level of $P < 0.05$, with a sample size of $n = 8$, was considered. Statistical significance was denoted as follows: $^{*}P < 0.05$, $^{**}P < 0.01$ compared to the CTL group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared to the T2D group

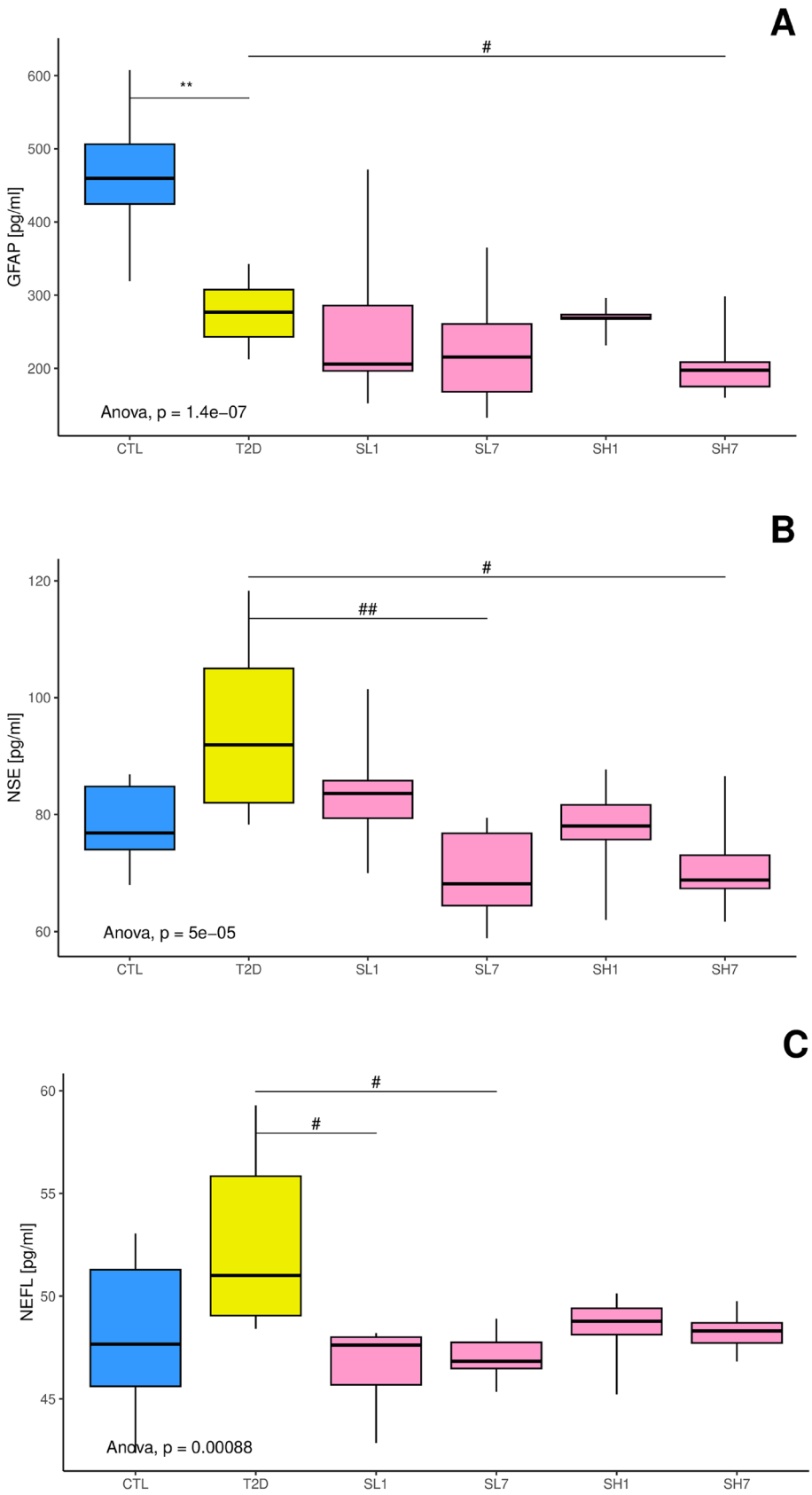
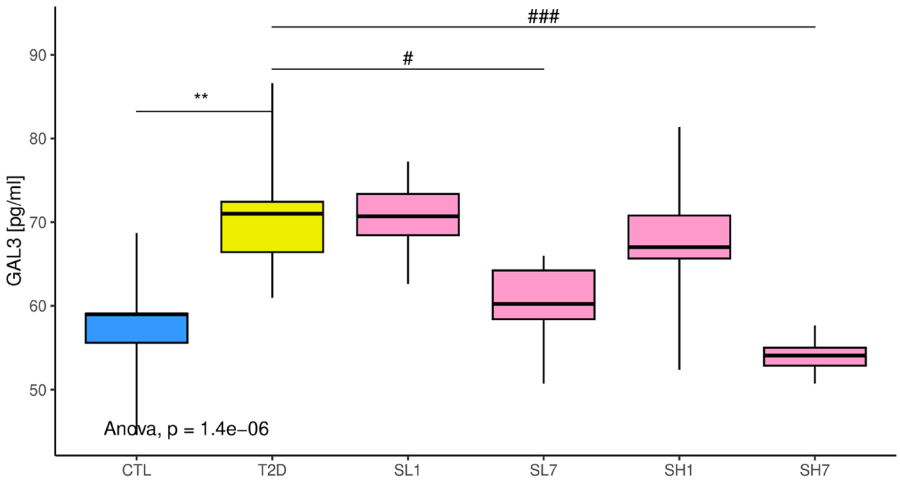


Fig. 2 Assessing semaglutide's impact on neurochemical markers in the cortex of T2D mice displaying anxiety- or depression-like behaviors. **A** glial fibrillary acidic protein (GFAP) level, **B** neuron specific enolase (NSE) level, **C** Neurofilament light chain (NEFL) level, D: Galectin-3 (GAL3) level. CTL: control mice, T2D: mice with diabetes; SL1: diabetic animals receiving a lower dose of semaglutide once weekly; SL7: diabetic animals receiving a lower dose of semaglutide once daily for 14 days; SH1: diabetic animals receiving high dose semaglutide once weekly; SH7: diabetic mice receiving a higher dose of semaglutide once daily for 14 days. The statistical analysis employed one-way ANOVA in conjunction with multiple comparison tests using the Student t-test with Bonferroni correction. A significance level of $P < 0.05$, with a sample size of $n = 8$, was considered. Statistical significance was denoted as follows: $^{**}P < 0.01$ compared to the CTL group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ compared to the T2D group

Fig. 2 (continued)



as a significant factor ($F_{(1,43)}=9.13$, $P<0.01$), this discovery bears little weight considering the overall lack of significance observed on the tested parameter. Furthermore, no notable alterations were detected in LKYN levels across all administered tests (Fig. 3C), as well as in the [LKYN/[TRP] ratio, irrespective of drug administration frequency or dosage (Fig. 3D).

Assessment of Blood Serum Biochemical Parameters in Type 2 Diabetic Mice with Anxiety or Depression Treated with Semaglutide

In the group of diabetic mice, significantly reduced levels of magnesium in blood serum were observed ($F_{(1,43)}=112$, $P<0.001$), the concentration of which did not significantly change despite the administration of semaglutide ($F_{(1,43)}=0.000159$, $P>0.1$) (Fig. 4A). Although ANOVA identifies dosage frequency as a significant effect ($F_{(1,43)}=4.54$, $P<0.05$, this fact cannot be treated as important, as the overall drug effect is not significant. Diabetes animals had significantly higher levels of CRP ($F_{(1,43)}=18.4$, $P<0.001$) and this level was significantly decreased back by administering drug ($F_{(1,43)}=11.3$, $P<0.01$) (Fig. 4B). Comparing dosages and frequency of drug administration, it can be concluded that higher dose worked significantly better ($F_{(1,43)}=15.1$, $P<0.001$), whereas the frequency of drug administration did not make a significant difference ($F_{(1,43)}=1.9$, $P>0.1$). Multiple comparison test proves this conclusion because significant differences are observed between the T2D group and both groups of higher doses.

Discussion

Metabolic disorders associated with diabetes can intricately alter the neurochemical landscape of the brain, setting the stage for anxiety and depressive behaviors through multifaceted pathways. Variations in glucose levels, vascular impairment, chronic inflammation, and oxidative stress foster an environment that disrupts neurotransmitter function, ultimately influencing mood regulation. Our previous research has established a significant correlation between neuroinflammation and cognitive impairments in a mouse model of type 2 diabetes (Piatkowska-Chmiel et al. 2021, 2022a, 2022b). We uncovered the intricate interplay between central nervous system inflammation- and cognitive dysfunction demonstrating an inflammatory process in both central and peripheral regions in diabetic mice. Notably, there was a significant increase in peripheral C-reactive protein (CRP) and elevated levels of GAL3 in the brain, a critical marker of neuroinflammatory diseases (García-Revilla et al. 2022). General inflammation can disturb neurochemical equilibrium and impair the functioning of brain regions essential for mood regulation (Osimo et al. 2019), potentially precipitating depressive symptoms such as low mood, fatigue, and reduced interest or pleasure (Maes et al. 2012). Our results indicate a potential link between the pro-inflammatory effects of GAL3 and anxiety and depression-like behavior in type 2 diabetic mice. Stajic et al. (2019) demonstrated that mice

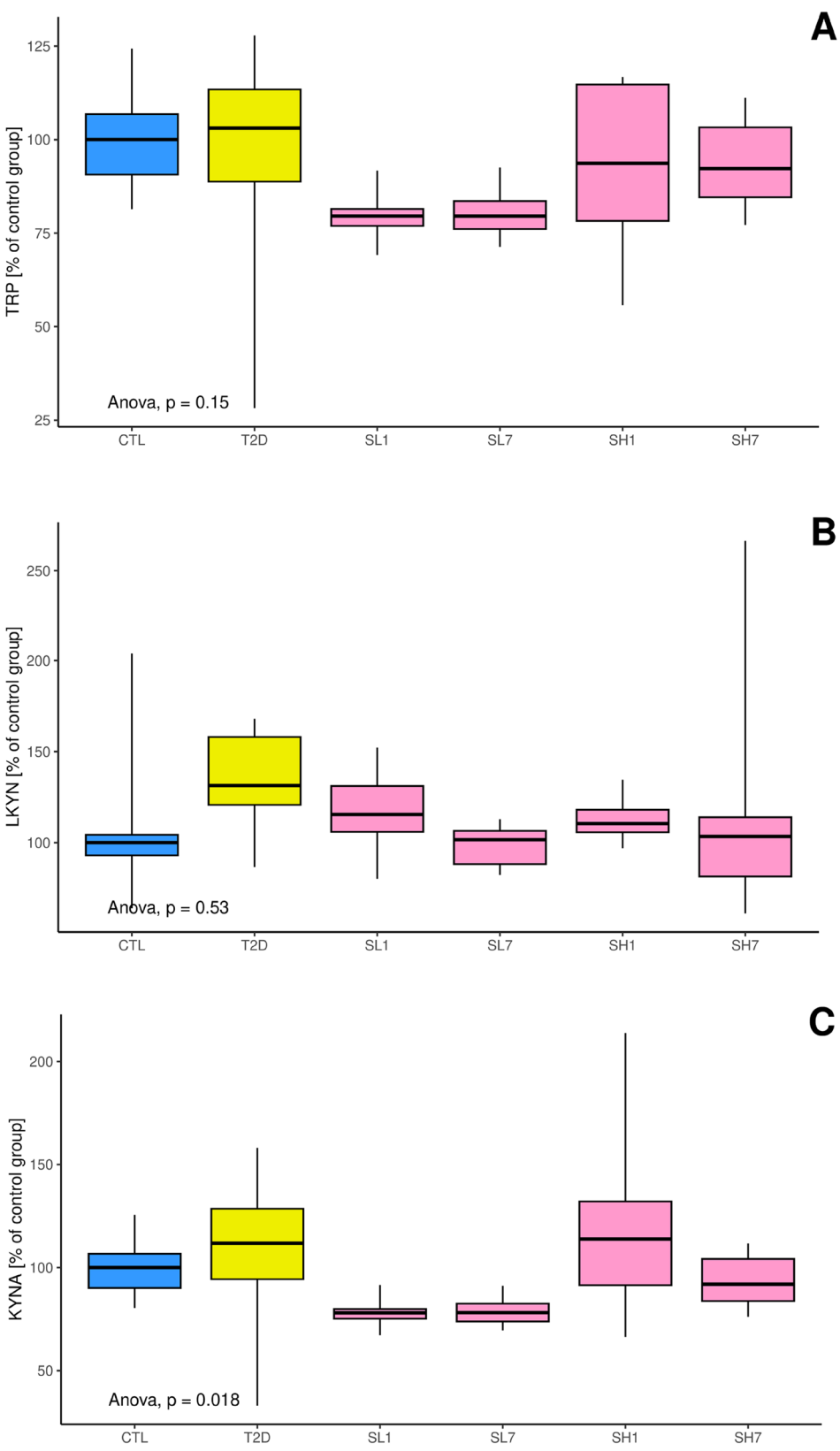
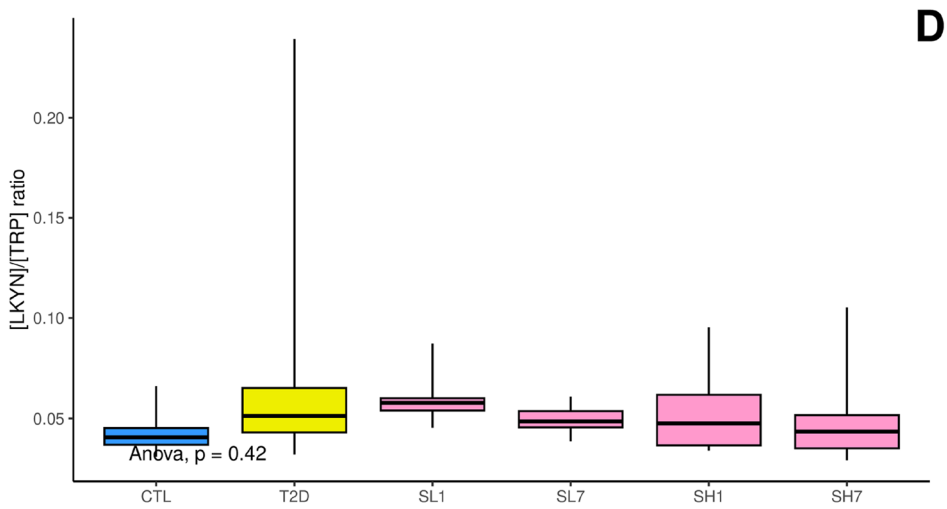
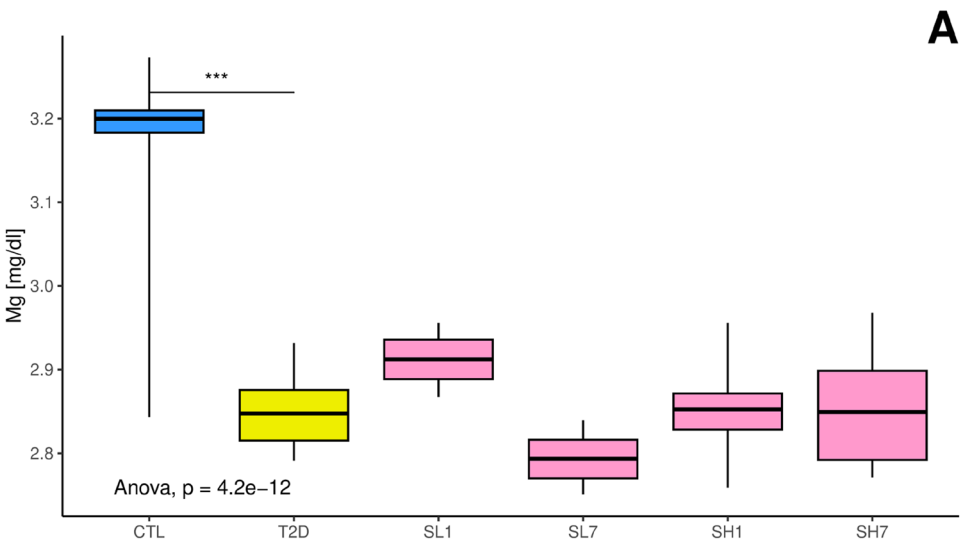


Fig. 3 Cortical levels of TRP, LKYN, KYNA, and LKYN/TRP ratio in T2D mice: impact of subcutaneous semaglutide administration across therapeutic regimens. **A** Tryptophan (TRP) level, **B** kynurenine (LKYN) level, **C** kynurenic acid (KYNA), D: LKYN/TRP ratio; CTL: control mice, T2D: mice with diabetes; SL1: diabetic animals receiving a lower dose of semaglutide once weekly; SL7: diabetic animals receiving a lower dose of semaglutide once daily for 14 days; SH1: diabetic animals receiving high dose semaglutide once weekly; SH7: diabetic mice receiving a higher dose of semaglutide once daily for 14 days. The statistical analysis employed one-way ANOVA in conjunction with multiple comparison tests using the Student t-test with Bonferroni correction. A significance level of $P < 0.05$, with a sample size of $n = 8$, was considered

Fig. 3 (continued)





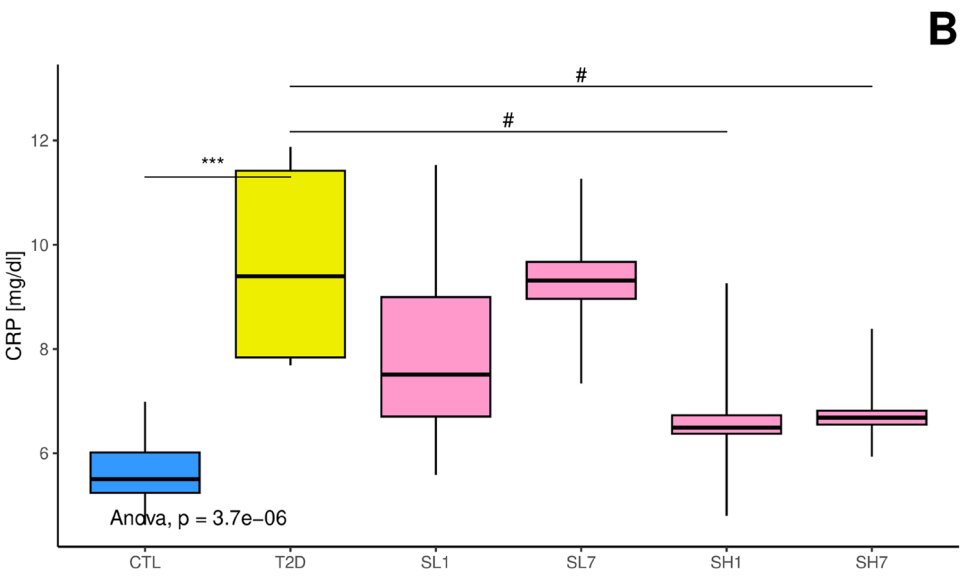


Fig. 4 The effect of semaglutide on biochemical parameters in blood serum of type 2 diabetic mice exhibiting anxiety-like or depressive-like behavior. **A** magnesium (Mg) level, **B** C-reactive protein (CRP) level. CTL: control mice, T2D: mice with diabetes; SL1: diabetic animals receiving a lower dose of semaglutide once weekly; SL7: diabetic animals receiving a lower dose of semaglutide once daily for 14 days; SH1: diabetic animals receiving high dose semaglutide once weekly; SH7: diabetic mice receiving a higher dose of semaglutide once daily for 14 days. The statistical analysis employed one-way ANOVA in conjunction with multiple comparison tests using the Student t-test with Bonferroni correction. A significance level of $P < 0.05$, with a sample size of n = 8, was considered. Statistical significance was denoted as follows: $^{***}P < 0.001$ compared to the CTL group; $^{\#}P < 0.05$ compared to the T2D group

experiencing LPS-induced neuroinflammation exhibited diminished exploratory locomotor activity, anhedonia, and anxiety-like behavior. Furthermore, the reduction of GAL3 in these mice reduced neuroinflammation-associated anxiety levels (Stajic et al. 2019), which is also consistent with our observations. Notably, semaglutide treatment correlated with decreased GAL3 levels in the cerebral cortex and improved behavioral outcomes. After two weeks of daily semaglutide administration, we observed modulation of NSE levels in the brains of treated diabetic animals, leading to enhanced exploratory activity and reduced anxiety and depressive behaviors. This suggests that the antidepressant effects of semaglutide, via GLP-1 receptor activation, may be closely linked to its neuroprotective and anti-inflammatory properties. Hence, it appears that the antidepressant effects resulting from GLP-1 receptor activation by semaglutide may be deeply intertwined with its ability to mitigate neurodegeneration and inflammation. Mounting evidence indicates that GLP-1 analogs are pivotal in stimulating the production of anti-inflammatory cytokines throughout various organs, notably within the brain. Studies on Alzheimer's disease models, demonstrated significant reductions in neuroinflammation following treatment with exenatide-4 (20 µg/kg/day) (Solmaz et al. 2015) and liraglutide (25 nmol/kg/day) (McClean et al. 2011). Considering the distribution of GLP-1 receptors (GLP-1R) in brain regions associated with mood regulation (Sharma et al. 2015), these analogs may enhance neurotransmitter release, such as serotonin and dopamine, in critical brain areas like the cerebral cortex and hippocampus (Rebosio et al. 2018), indicating their potential to alleviate anxiety and depression-related behaviors. Our study reinforces the efficacy of chronic semaglutide administration in mitigating anxiety-like and depressive behaviors in diabetic mice while revealing significant neurobiological changes in the cerebral cortex. Furthermore, our investigation revealed significant neurobiological changes within the cerebral cortex of diabetic animals. Specifically, we noted a marked decrease in GFAP levels, which may result from increased blood–brain barrier permeability and oxidative stress in the central nervous system's microcapillaries due to diabetes (Ayala-Guerrero et al. 2022). Research indicates reduced glial cell density in major depression (MDD), particularly in the dorsolateral prefrontal cortex, correlating with lower GFAP levels (Si et al. 2004). Moreover, postmortem analyses of brain structures from individuals who died by suicide showed astrocytic irregularities, including reduced levels of GFAP mRNA and protein in mood-regulating regions like the medial thalamus and caudate nucleus. These regions are pivotal in mood regulation (Torres-Platas et al. 2016). Interestingly, postmortem biopsies from depressed patients treated with psychotropic drugs exhibited higher GFAP expression than untreated individuals (Cobb et al. 2016). In contrast, our study found no changes were observed in GFAP levels in the cerebral cortex of semaglutide-treated mice compared to diabetic controls, suggesting reducted leakage of this protein across the blood–brain barrier. Research by Timper et al. (2020) indicates that GLP-1R signaling is essential for mitochondrial integrity and function in astrocytes, influencing energy and glucose homeostasis. However, we were unable to determine the reason for the decreased GFAP levels in the cerebral cortex of mice receiving a higher dose of semaglutide over 14 days despite extensive analysis.

Research shows, that in diabetes, low-grade inflammation might trigger heightened indoleamine 2,3-dioxygenase (IDO) activity, leading to an accelerating tryptophan metabolism along the kynurenine pathway, potentially leading to serotonin deficit, that impact mood, emotional regulation, and sleep cycles (Hestad et al. 2022). Abnormal kynurenine have been observed in patients with major depression, anxiety disorders, or schizophrenia (Paul et al. 2022; Butler et al. 2022; Oxenkrug et al. 2016). diabetic Although previous studies have shown alterations in the tryptophan-kynurenine pathway in animal models (Dias et al., 2015; Chmiel-Perzyńska et al. 2014), our study did not report significant changes in the levels of tryptophan, kynurenine, and kynurenic acid levels in the diabetic animals. Hyperglycemia and elevated D, L-homocysteine concentration, may disrupt kynurenic acid synthesis in the brain of diabetic animals, leading to central complications, (Chmiel-Perzyńska et al. 2007). Additionally, Chmiel-Perzyńska et al. (2014) found that the concentration of KYNA is elevated in the hippocampus of streptozotocin-induced diabetic rats, but not in the cortex or striatum, aligning with our findings. Moreover, an elevated LKYN/TRP ratio in type II diabetes, particularly with poor glycemic control, suggests increased IDO activity (Abedi et al. 2021). Our study noted a trend towards a higher LKYN/TRP ratio in diabetic mice, though it did not achieve statistical significance. In contrast, mice receiving daily semaglutide treatment for two weeks exhibited an LKYN/TRP ratio comparable to healthy controls, likely due to effective glycemic regulation. It is tempting to speculate that prolongation of the semaglutide administration time could effectively regulate the kynurenine pathway. Pharmacological modulation of the kynurenine pathway, particularly by enhancing KYNA production, could exert profound effects on neurochemical balance and central nervous system function. Interestingly, neither tryptophan nor kynurenine nor kynureninic acid concentrations correlated with CRP or GAL3 concentrationssuggesting a complex interplay between inflammatory markers and kynurenine pathway metabolites that warrants further investigation.

Recent research suggests that elevated levels of NSE in the serum and cerebrospinal fluid of patients with major

depressive disorder can directly correlate with neuronal damage (Haque et al. 2018), with NSE contributing to redox imbalance, neuroinflammation and mitochondrial dysfunction,. In turn, neuroaxonal damage which is also associated with major depressive disorder, is associated with the release of neurofilament light chain serving as one of the markers for this pathological process (Chen et al. 2022). While diabetic mice showed a trend toward higher NSE and NEFL levels, these changes were not statistically significant, but may signal early neuronal or axonal damage. Semaglutide treatment for two weeks modulated NSE levels, influencing behavioral responses and inflammatory pathways. Interestingly, regardless of the dose and frequency of semaglutide administration, there was no significant increase in NEFL concentration within the mouse brain over the 2-week treatment period, suggesting the absence of progressive neuronal damage across all treatment groups. Notably, the most substantial decrease in the level of neurofilament light chain was observed in groups receiving the drug at lower doses either once weekly or daily for the 14-day duration. The alterations in NEFL concentration correlated with a decrease in peripheral C-reactive protein (CRP) levels, implying a connection between NEFL and systemic inflammation.

Another significant parameter that plays a vital role in regulating mood is magnesium. Hypomagnesemia is a common phenomenon in patients with type 2 diabetes, especially in those with a poorly controlled glycemic profile (Barbagallo and Dominguez 2015). Our research also confirms this association, showing a significant magnesium deficiency in animal model of type 2 diabetes. Magnesium deficiency can intensify the body's stress response, contributing to increased anxiety and depression by disrupting neurotransmitter function and impairing the regulation of the hypothalamic–pituitary–adrenal (HPA) axis, which plays a critical role in managing stress (Serefko et al. 2013; Moabedi et al. 2023). The absence of this essential microelement may result in heightened inflammation and the activation of phagocytic cells, consequently triggering the generation of reactive oxygen species (Libako et al. 2010). Our research findings provide further evidence by confirming a correlation between the level of magnesium in blood serum and the overall inflammatory state in diabetic mice. Moreover, magnesium ions play a crucial role inregulating calcium ion flow through neuronal calcium channels, which directly impacts the production of neuronal nitric oxide. Disruptions in these processes can lead to neuronal dysfunction, potentially contributing to the development of mental disorders like depression or anxiety (Nielsen 2018).

Our study faced several significant limitations. Firstly, the restricted number of animals within experimental groups may have compromised the overall representativeness of the obtained results, leading to greater fluctuations in the outcomes. Secondly, semaglutide therapy was used only for two weeks, which is a significant limitation in the context of assessing the long-term effects of treatment, especially for central nervous system disorders. The relatively short treatment timeframe may not have been sufficient to fully capture the range of therapeutic benefits or potential adverse effects associated with prolonged use. This limitation may also explain the lack of significant, measurable changes in key metabolites such as TRP, KYNA, and LKYN, which are critical components of the kynurenine pathway. It is well recognized that certain biochemical pathways, especially those related to mood regulation, often require extended pharmacological intervention before meaningful shifts become apparent. However, considering the unexpectedly promising results of our research, we felt it was essential to share our findings with a broader scientists. Ultimately, transferring the results from our animal study to clinical practice requires in-depth research. It is crucial to understand the mechanisms of action of the drug and its impact on the human body in various clinical conditions. For this reason, future research should focus on the long-term effectiveness and safety of semaglutide therapy in patients with type 2 diabetes, as well as the possible impact on their mental status and overall quality of life. Only after thoroughly examining these issues will we be able to fully assess the neuroprotective potential of semaglutide as an effective tool in the comprehensive treatment of patients affected by this disease.

In conclusion, our study highlights the significant therapeutic potential of semaglutide in improving both behavioral patterns and neurochemical markers in diabetic mice. Notably, we found that the frequency of administration emerged as a crucial factor influencing the observed effects, whereas the dose size showed secondary importance. Despite the fact that our experiments were conducted in mice, the kynurenine pathway, along with neurochemical markers such as GFAP, NSE, and NEFL, may have important implications for understanding neuropsychiatric and metabolic disorders in humans with diabetes and depression. The relationship between these neurochemical markers and the kynurenine pathway underscores a promising avenue for future research, emphasizing how these biological indicators can enhance clinical practices. By monitoring fluctuations in these markers, clinicians may better identify patients at risk for developing mood disorders linked to metabolic dysfunction and evaluate the effectiveness of therapeutic interventions. Further research in this area could uncover new biomarkers that may serve as indicators of the effectiveness of therapeutic interventions and facilitate the identification of patients who are most vulnerable to mood disorders associated with diabetes. This proactive approach may pave the way for personalized treatment strategies aimed at alleviating anxiety and

depression in diabetic patients by concurrently addressing both metabolic and neuroinflammatory pathways. Ultimately, this strategy could significantly enhance mental health and overall well-being in individuals with diabetes.

Data Availability Statement

Data is provided within the manuscript or supplementary information files.

Author Contributions I.P.Ch. designed the studies. I.P.Ch., K.P., A.S. performed the experiments, analyzed the data, and assisted with drafting the manuscript, M.H. and K.W.K. interpreted the data and contributed to drafting the manuscript. T.K. assisted with manuscript editing, while K.W.K. and K.P. designed the figures. J.D. and M.H. supervised the project, provided guidance in interpreting the results, and contributed to the final version of the manuscript. All authors collaborated in writing and editing the manuscript. Furthermore, all authors critically reviewed and revised the manuscript, giving their approval for the final version of the article.

Funding The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Statutory Activity of the Medical University of Lublin, Poland (Grant No. DS38/2024).

Data Availability The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality agreements. However, they can be made available by the corresponding author upon reasonable request, ensuring compliance with applicable regulations.

Declarations

Conflict of Interest The authors declare no competing interests.

Institutional Review Board Statement The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee for Animal Research (No. 43/2018, 26 March 2018).

Informed Consent Statement Not applicable.

References

Abedi S, Vessal M, Asadian F, Takhshid MA (2021) Association of serum kynurenine/tryptophan ratio with poor glycemic control in patients with type2 diabetes. J Diabetes Metab Disord 20(2):1521–1527. https://doi.org/10.1007/s40200-021-00895-z

Anderberg RH, Richard JE, Hansson C, Nissbrandt H, Bergquist F, Skibicka KP (2016) GLP-1 is both anxiogenic and antidepressant; divergent effects of acute and chronic GLP-1 on emotionality. Psychoneuroendocrinology 65:54–66. https://doi.org/10.1016/j.psyneuen.2015.11.021

Ara I, Bano S (2012) Citalopram decreases tryptophan 2,3-dioxygenase activity and brain 5-HT turnover in swim stressed rats. Pharmacol Rep 64(3):558–566. https://doi.org/10.1016/s1734-1140(12)70851-4

Ayala-Guerrero L, García-delaTorre P, Sánchez-García S, Guzmán-Ramos K (2022) Serum levels of glial fibrillary acidic protein association with cognitive impairment and type 2 diabetes. Arch Med Res 53(5):501–507. https://doi.org/10.1016/j.arcmed.2022.06.001

Bădescu SV, Tătaru C, Kobylinska L, Georgescu EL, Zahiu DM, Zăgrean AM, Zăgrean L (2016) The association between diabetes mellitus and depression. J Med Life 9(2):120–125

Barbagallo M, Dominguez LJ (2015) Magnesium and type 2 diabetes. World World J Diabetes 6(10):1152–1157. https://doi.org/10.4239/wjd.v6.i10.1152

Batista AF, Bodart-Santos V, De Felice FG, Ferreira ST (2019) Neuroprotective actions of glucagon-like peptide-1 (GLP-1) analogues in Alzheimer's and Parkinson's diseases. CNS Drugs 33(3):209–223. https://doi.org/10.1007/s40263-018-0593-6

Bradford MM (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 72:248–254. https://doi.org/10.1006/abio.1976.9999

Butler MI, Long-Smith C, Moloney GM, Morkl S, O'Mahony SM, Cryan JF, Clarke G, Dinan TG (2022) The immune-kynurenine pathway in social anxiety disorder. Brain Behav Immun 99:317–326. https://doi.org/10.1016/j.bbi.2021.10.020

Chen MH, Liu YL, Kuo HW, Tsai SJ, Hsu JW, Huang KL, Tu PC, Bai YM (2022) Neurofilament light chain is a novel biomarker for major depression and related executive dysfunction. Int J Neuropsychopharmacol 25(2):99–105. https://doi.org/10.1093/ijnp/pyab068

Chmiel-Perzyńska I, Perzyński A, Wielosz M, Urbańska EM (2007) Hyperglycemia enhances the inhibitory effect of mitochondrial toxins and D,L-homocysteine on the brain production of kynurenic acid. Pharmacol Rep 59(3):268–273

Chmiel-Perzyńska I, Perzyński A, Urbańska EM (2014) Experimental diabetes mellitus type 1 increases hippocampal content of kynurenic acid in rats. Pharmacol Rep 66(6):1134–1139. https://doi.org/10.1016/j.pharep.2014.07.014

Cobb JA, O'Neill K, Milner J, Mahajan GJ, Lawrence TJ, May WL, Miguel-Hidalgo J, Rajkowska G, Stockmeier CA (2016) Density of GFAP-immunoreactive astrocytes is decreased in left hippocampi in major depressive disorder. Neuroscience 316:209–220. https://doi.org/10.1016/j.neuroscience.2015.12.044

da Silva Dias IC, Carabelli B, Ishii DK, de Morais H, de Carvalho MC, Rizzo de Souza LE, Zanata SM, Brandão ML, Cunha TM, Ferraz AC, Cunha JM, Zanoveli JM (2016) Indoleamine-2,3-dioxygenase/kynurenine pathway as a potential pharmacological target to treat depression associated with diabetes. Mol Neurobiol 53(10):6997–7009. https://doi.org/10.1007/s12035-015-9617-0

Detka J, Kurek A, Kucharczyk M, Głombik K, Basta-Kaim A, Kubera M, Lasoń W, Budziszewska B (2015) Brain glucose

metabolism in an animal model of depression. Neuroscience 295:198–208. https://doi.org/10.1016/j.neuroscience.2015.03.046

Duarte AI, Candeias E, Alves IN, Mena D, Silva DF, Machado NJ, Campos EJ, Santos MS, Oliveira CR, Moreira PI (2020) Liraglutide protects against brain amyloid-β_{1-42} accumulation in female mice with early Alzheimer's disease-like pathology by partially rescuing oxidative/nitrosative stress and inflammation. Int J Mol Sci 21(5):1746. https://doi.org/10.3390/ijms21051746

Dudek KA, Dion-Albert L, Lebel M, LeClair K, Labrecque S, Tuck E, Ferrer Perez C, Golden SA, Tamminga C, Turecki G, Mechawar N, Russo SJ, Menard C (2020) Molecular adaptations of the blood-brain barrier promote stress resilience vs. depression. Proc Natl Acad Sci USA 117(6):3326–3336. https://doi.org/10.1073/pnas.1914655117

Dziewa M, Bańka B, Herbet M, Piątkowska-Chmiel I (2023) Eating disorders and diabetes: facing the dual challenge. Nutrients 15(18):3955. https://doi.org/10.3390/nu15183955

Franklin M, Bermudez I, Murck H, Singewald N, Gaburro S (2012) Sub-chronic dietary tryptophan depletion–an animal model of depression with improved face and good construct validity. J Psychiatr Res 46(2):239–247. https://doi.org/10.1016/j.jpsychires.2011.10.003

García-Revilla J, Boza-Serrano A, Espinosa-Oliva AM, Soto MS, Deierborg T, Ruiz R, de Pablos RM, Burguillos MA, Venero JL (2022) Galectin-3, a rising star in modulating microglia activation under conditions of neurodegeneration. Cell Death Dis 13(7):628. https://doi.org/10.1038/s41419-022-05058-3

Gil-Lozano M, Pérez-Tilve D, Alvarez-Crespo M, Martís A, Fernandez AM, Catalina PA, Gonzalez-Matias LC, Mallo F (2010) GLP-1(7–36)-amide and Exendin-4 stimulate the HPA axis in rodents and humans. Endocrinology 151(6):2629–2640. https://doi.org/10.1210/en.2009-0915

Głombik K, Detka J, Kurek A, Budziszewska B (2020) Impaired brain energy metabolism: involvement in depression and hypothyroidism. Front Neurosci 14:586939. https://doi.org/10.3389/fnins.2020.586939

Gold PW, Goodwin FK, Chrousos GP (1988) Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (1). N Engl J Med 319(6):348–353. https://doi.org/10.1056/NEJM198808113190606

Hall C. S., Ballachey E. L., 1932. A study of the rat's behavior in a field. A contribution to method in comparative psychology, vol 6. University of California Publications in Psychology, Berkeley, pp 1–12

Haque A, Polcyn R, Matzelle D, Banik NL (2018) New insights into the role of neuron-specific enolase in neuro-inflammation, neurodegeneration, and neuroprotection. Brain Sci 8(2):33. https://doi.org/10.3390/brainsci8020033

Hestad K, Alexander J, Rootwelt H, Aaseth JO (2022) The role of tryptophan dysmetabolism and quinolinic acid in depressive and neurodegenerative diseases. Biomolecules 12(7):998. https://doi.org/10.3390/biom12070998

Katsurada K, Yada T (2016) Neural effects of gut- and brain-derived glucagon-like peptide-1 and its receptor agonist. J Diabetes Investig 7(Suppl 1):64–69. https://doi.org/10.1111/jdi.12464

Kegel ME, Bhat M, Skogh E, Samuelsson M, Lundberg K, Dahl ML, Sellgren C, Schwieler L, Engberg G, Schuppe-Koistinen I, Erhardt S (2014) Imbalanced kynurenine pathway in schizophrenia. Int J Tryptophan Res 7:15–22. https://doi.org/10.4137/IJTR.S16800

Kim YK, Kim OY, Song J (2020) Alleviation of depression by glucagon-like peptide 1 through the regulation of neuroinflammation, neurotransmitters, neurogenesis, and synaptic function. Front Pharmacol 11:1270. https://doi.org/10.3389/fphar.2020.01270

Libako P, Nowacki W, Rock E, Rayssiguier Y, Mazur A (2010) Phagocyte priming by low magnesium status: input to the enhanced inflammatory and oxidative stress responses. Magnes Res 23(1):1–4. https://doi.org/10.1684/mrh.2009.0201

Liu W, Ge T, Leng Y, Pan Z, Fan J, Yang W, Cui R (2017) The role of neural plasticity in depression: from hippocampus to prefrontal cortex. Neural Plast 2017:6871089. https://doi.org/10.1155/2017/6871089

Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R (2011) The new "5-HT" hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry 35(3):702–721. https://doi.org/10.1016/j.pnpbp.2010.12.017

Maes M, Berk M, Goehler L, Song C, Anderson G, Gałecki P, Leonard B (2012) Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. BMC Med 10:66. https://doi.org/10.1186/1741-7015-10-66

Malhi GS, Mann JJ (2018) Depression. Lancet 392(10161):2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2

Mansur RB, Lee Y, Subramaniapillai M, Brietzke E, McIntyre RS (2018) Cognitive dysfunction and metabolic comorbidities in mood disorders: A repurposing opportunity for glucagon-like peptide 1 receptor agonists? Neuropharmacology 136(Pt B):335–342. https://doi.org/10.1016/j.neuropharm.2018.01.048

McClean PL, Parthsarathy V, Faivre E, Hölscher C (2011) The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci 31(17):6587–6594. https://doi.org/10.1523/JNEUROSCI.0529-11.2011

McClean PL, Jalewa J, Hölscher C (2015) Prophylactic liraglutide treatment prevents amyloid plaque deposition, chronic inflammation and memory impairment in APP/PS1 mice. Behav Brain Res 293:96–106. https://doi.org/10.1016/j.bbr.2015.07.024

Milaneschi Y, Simmons WK, van Rossum EFC, Penninx BW (2019) Depression and obesity: evidence of shared biological mechanisms. Mol Psychiatry 24(1):18–33. https://doi.org/10.1038/s41380-018-0017-5

Moabedi M, Aliakbari M, Erfanian S, Milajerdi A (2023) Magnesium supplementation beneficially affects depression in adults with depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Front Psych 14:1333261. https://doi.org/10.3389/fpsyt.2023.1333261

Myint AM, Schwarz MJ, Müller N (2012) The role of the kynurenine metabolism in major depression. J Neural Transm (Vienna) 119(2):245–251. https://doi.org/10.1007/s00702-011-0741-3

Nielsen FH (2018) Magnesium deficiency and increased inflammation: current perspectives. J Inflamm Res 11:25–34. https://doi.org/10.2147/JIR.S136742

Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM (2019) Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol Med 49(12):1958–1970. https://doi.org/10.1017/S0033291719001454

Owji AA, Khoshdel Z, Sanea F, Panjehshahin MR, Shojaee Fard M, Smith DM, Coppock HA, Ghatei MA, Bloom SR (2002) Effects of intracerebroventricular injection of glucagon like peptide-1 and its related peptides on serotonin metabolism and on levels of amino acids in the rat hypothalamus. Brain Res 929(1):70–75. https://doi.org/10.1016/s0006-8993(01)03379-0

Oxenkrug G, van der Hart M, Roeser J, Summergrad P (2016) Anthranilic acid: a potential biomarker and treatment target for schizophrenia. Ann Psychiatry Ment Health 4(2):1059

Paul ER, Schwieler L, Erhardt S, Boda S, Trepci A, Kämpe R, Asratian A, Holm L, Yngve A, Dantzer R, Heilig M, Hamilton JP, Samuelsson M (2022) Peripheral and central kynurenine pathway abnormalities in major depression. Brain Behav Immun 101:136–145. https://doi.org/10.1016/j.bbi.2022.01.002

Piatkowska-Chmiel I, Herbet M, Gawronska-Grzywacz M, Ostrowska-Lesko M, Dudka J (2021) The role of molecular and inflammatory indicators in the assessment of cognitive dysfunction in a mouse model of diabetes. Int J Mol Sci 22(8):3878. https://doi.org/10.3390/ijms22083878

Piątkowska-Chmiel I, Gawrońska-Grzywacz M, Popiołek Ł, Herbet M, Dudka J (2022a) The novel adamantane derivatives as potential mediators of inflammation and neural plasticity in diabetes mice with cognitive impairment. Sci Rep 12(1):6708. https://doi.org/10.1038/s41598-022-10187-y

Piątkowska-Chmiel I, Herbet M, Gawrońska-Grzywacz M, Dudka J (2022b) Regulation of neuroinflammatory signaling by PPARγ agonist in mouse model of diabetes. Int J Mol Sci 23(10):5502. https://doi.org/10.3390/ijms23105502

Porsolt RD, Le Pichon M, Jalfre M (1977) Depression: a new animal model sensitive to antidepressant treatments. Nature 266(5604):730–732. https://doi.org/10.1038/266730a0

Qin Y, Wang N, Zhang X, Han X, Zhai X, Lu Y (2018) IDO and TDO as a potential therapeutic target in different types of depression. Metab Brain Dis 33(6):1787–1800. https://doi.org/10.1007/s11011-018-0290-7

Quak J, Doornbos B, Roest AM, Duivis HE, Vogelzangs N, Nolen WA, Penninx BW, Kema IP, de Jonge P (2014) Does tryptophan degradation along the kynurenine pathway mediate the association between pro-inflammatory immune activity and depressive symptoms? Psychoneuroendocrinology 45:202–210. https://doi.org/10.1016/j.psyneuen.2014.03.013

Rebosio C, Balbi M, Passalacqua M, Ricciarelli R, Fedele E (2018) Presynaptic GLP-1 receptors enhance the depolarization-evoked release of glutamate and GABA in the mouse cortex and hippocampus. BioFactors 44(2):148–157. https://doi.org/10.1002/biof.1406

Réus GZ, Jansen K, Titus S, Carvalho AF, Gabbay V, Quevedo J (2015) Kynurenine pathway dysfunction in the pathophysiology and treatment of depression: evidences from animal and human studies. J Psychiatr Res 68:316–328. https://doi.org/10.1016/j.jpsychires.2015.05.007

Savitz J, Drevets WC, Smith CM, Victor TA, Wurfel BE, Bellgowan PS, Bodurka J, Teague TK, Dantzer R (2015) Putative neuroprotective and neurotoxic kynurenine pathway metabolites are associated with hippocampal and amygdalar volumes in subjects with major depressive disorder. Neuropsychopharmacology 40(2):463–471. https://doi.org/10.1038/npp.2014.194

Semenkovich K, Brown ME, Svrakic DM, Lustman PJ (2015) Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. Drugs 75(6):577–587. https://doi.org/10.1007/s40265-015-0347-4

Serefko A, Szopa A, Wlaź P, Nowak G, Radziwoń-Zaleska M, Skalski M, Poleszak E (2013) Magnesium in depression. Pharmacol Rep: PR 65(3):547–554. https://doi.org/10.1016/s1734-1140(13)71032-6

Sharma AN, Ligade SS, Sharma JN, Shukla P, Elased KM, Lucot JB (2015) GLP-1 receptor agonist liraglutide reverses long-term atypical antipsychotic treatment associated behavioral depression and metabolic abnormalities in rats. Metab Brain Dis 30(2):519–527. https://doi.org/10.1007/s11011-014-9591-7

Si X, Miguel-Hidalgo JJ, O'Dwyer G, Stockmeier CA, Rajkowska G (2004) Age-dependent reductions in the level of glial fibrillary acidic protein in the prefrontal cortex in major depression. Neuropsychopharmacology 29(11):2088–2096. https://doi.org/10.1038/sj.npp.1300525

Slattery DA, Cryan JF (2012) Using the rat forced swim test to assess antidepressant-like activity in rodents. Nat Protoc 7(6):1009–1014. https://doi.org/10.1038/nprot.2012.044

Solmaz V, Çınar BP, Yiğittürk G, Çavuşoğlu T, Taşkıran D, Erbaş O (2015) Exenatide reduces TNF-α expression and improves hippocampal neuron numbers and memory in streptozotocin treated rats. Eur J Pharmacol 765:482–487. https://doi.org/10.1016/j.ejphar.2015.09.024

Stajic D, Selakovic D, Jovicic N, Joksimovic J, Arsenijevic N, Lukic ML, Rosic G (2019) The role of galectin-3 in modulation of anxiety state level in mice. Brain Behav Immun 78:177–187. https://doi.org/10.1016/j.bbi.2019.01.019

Steel JM, Young RJ, Lloyd GG, Clarke BF (1987) Clinically apparent eating disorders in young diabetic women: associations with painful neuropathy and other complications. Br Med J (Clin Res Ed) 294(6576):859–862. https://doi.org/10.1136/bmj.294.6576.859

Timper K, Del Río-Martín A, Cremer AL, Bremser S, Alber J, Giavalisco P, Varela L, Heilinger C, Nolte H, Trifunovic A, Horvath TL, Kloppenburg P, Backes H, Brüning JC (2020) GLP-1 receptor signaling in astrocytes regulates fatty acid oxidation, mitochondrial integrity, and function. Cell Metab 31(6):1189-1205.e13. https://doi.org/10.1016/j.cmet.2020.05.001

Torres-Platas SG, Nagy C, Wakid M, Turecki G, Mechawar N (2016) Glial fibrillary acidic protein is differentially expressed across cortical and subcortical regions in healthy brains and downregulated in the thalamus and caudate nucleus of depressed suicides. Mol Psychiatry 21(4):509–515. https://doi.org/10.1038/mp.2015.65

Trammell TS, Henderson NL, Madkour HS, Stanwood GD, Graham DL (2021) GLP-1R activation alters performance in cognitive tasks in a sex-dependent manner. Neurol Sci 42(7):2911–2919. https://doi.org/10.1007/s10072-020-04910-8

Velmurugan K, Balamurugan AN, Loganathan G, Ahmad A, Hering BJ, Pugazhenthi S (2012) Antiapoptotic actions of exendin-4 against hypoxia and cytokines are augmented by CREB. Endocrinology 153(3):1116–1128. https://doi.org/10.1210/en.2011-1895

Ventorp F, Bay-Richter C, Nagendra AS, Janelidze S, Matsson VS, Lipton J, Nordström U, Westrin Å, Brundin P, Brundin L (2017) Exendin-4 treatment improves LPS-induced depressive-like behavior without affecting pro-inflammatory cytokines. J Parkinsons Dis 7(2):263–273. https://doi.org/10.3233/JPD-171068

Weina H, Yuhu N, Christian H, Birong L, Feiyu S, Le W (2018) Liraglutide attenuates the depressive- and anxiety-like behaviour in the corticosterone induced depression model via improving hippocampal neural plasticity. Brain Res 1694:55–62. https://doi.org/10.1016/j.brainres.2018.04.031

Winzeler B, da Conceição I, Refardt J, Sailer CO, Dutilh G, Christ-Crain M (2019) Effects of glucagon-like peptide-1 receptor agonists on hypothalamic-pituitary-adrenal axis in healthy volunteers. J Clin Endocrinol Metab 104(1):202–208. https://doi.org/10.1210/jc.2018-01420

Zhao J, Gao P, Zhu D (2010) Optimization of Zn2+-containing mobile phase for simultaneous determination of kynurenine, kynurenic acid and tryptophan in human plasma by high performance liquid chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 878(5–6):603–608. https://doi.org/10.1016/j.jchromb.2010.01.006

Zhu X, Jing L, Chen C, Shao M, Fan Q, Diao J, Liu Y, Lv Z, Sun X (2015) Danzhi Xiaoyao San ameliorates depressive-like behavior by shifting toward serotonin via the downregulation of hippocampal indoleamine 2,3-dioxygenase. J Ethnopharmacol 160:86–93. https://doi.org/10.1016/j.jep.2014.11.031

Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM (2011) Glucocorticoids, cytokines and brain abnormalities in depression. Prog Neuropsychopharmacol Biol Psychiatry 35(3):722–729. https://doi.org/10.1016/j.pnpbp.2010.04.011

Zunszain PA, Hepgul N, Pariante CM (2013) Inflammation and depression. Curr Top Behav Neurosci 14:135–151. https://doi.org/10.1007/7854_2012_211