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Comparative effects of selective and non-selective sodium–glucose cotransporter inhibition on cognitive dysfunction in a rat model of type 2 diabetes

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ABSTRACT: Type 2 diabetes mellitus (T2DM) is increasingly recognized as a significant risk factor for cognitive decline and Alzheimer's disease (AD), yet the effects of antidiabetic agents on diabetes-related neurodegeneration are not fully understood. This study aimed to investigate the effects of the non-selective sodium-glucose cotransporter (SGLT) inhibitor phlorizin and the selective SGLT2 inhibitor dapagliflozin on metabolic and cognitive parameters in a rat model of T2DM-associated cognitive impairment (T2DM-CD). Sprague-Dawley rats were fed a high-fat diet and administered low-dose streptozotocin, followed by treatment with dapagliflozin, phlorizin, metformin, or rivastigmine for four weeks. Blood glucose, body weight, locomotor activity, and recognition memory were assessed using metabolic and behavioural tests. The T2DM-CD model showed hyperglycaemia without changes in locomotor activity and significant deficits in recognition memory. Dapagliflozin and phlorizin treatments significantly reduced blood glucose and improved recognition memory compared to the T2DM-CD model. Rivastigmine improved cognitive performance without affecting glycaemic control, while metformin improved glycaemic status and provided modest cognitive improvement. These findings suggest that SGLT inhibition may alleviate cognitive deficits in the T2DM-CD model and that SGLT inhibitors may exert beneficial effects on diabetes-related cognitive dysfunction through both metabolic and central mechanisms.

KEYWORDS: Type 2 diabetes mellitus; SGLT inhibitors; cognitive impairment; high-fat-diet; streptozotocin.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycaemia resulting from impaired insulin secretion, insulin resistance, or a combination of both processes [1]. Type 2 DM (T2DM) accounts for the vast majority of DM cases worldwide and has become a significant global health problem due to its increasing prevalence and association with increased morbidity [2]. Current data show that T2DM is quite common and is associated with numerous systemic complications and comorbidities [3].

In addition to these metabolic consequences, T2DM is also considered a significant risk factor for cognitive decline and dementia, including Alzheimer's disease (AD). Epidemiological studies and meta-analyses have demonstrated that individuals with T2DM are more likely to develop dementia compared with non-diabetic populations, with pooled estimates indicating approximately a 1.5–1.7-fold higher risk of dementia among patients with T2DM [4]. Chronic hyperglycaemia and associated insulin resistance are implicated in mechanisms that may accelerate neurodegenerative processes, including vascular dysfunction, oxidative stress, inflammation, and impaired neuronal insulin signalling—all of which have been proposed to contribute to dementia pathogenesis [5, 6].

Epidemiological data consistently show that cognitive impairment, including mild cognitive impairment and dementia, is more prevalent among individuals with T2DM. A systematic review and meta-analysis demonstrated that the prevalence of MCI in T2DM populations worldwide is high, with pooled estimates around 44–45%, underscoring the importance of careful monitoring of cognitive function in patients

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with T2DM [7, 8]. Moreover, large cohort and prospective observational studies have shown that T2DM is associated with an increased risk of dementia outcomes. For example, individuals with T2DM exhibit a significantly higher risk of all-cause dementia, including AD, compared with non-diabetic counterparts, with hazard ratios ranging from about 1.4 to greater than 1.6 in long-term follow-up studies [9, 10].

As the population ages, the prevalence of AD and other types of dementia is increasing. AD is the most common cause of dementia and leads to disability and caregiver dependency among older adults worldwide. Current epidemiological estimates reported in the 2024 World Alzheimer's Report [11] and the World Health Organization's (WHO) [12] assessments indicate that approximately 55 million people will be living with dementia in 2024. Due to demographic changes and increasing life expectancy, this number is projected to reach approximately 78 million by 2030 and approximately 139 million by 2050. AD is estimated to account for approximately 60-70% of all dementia diagnoses [13]. Given this rapidly increasing disease burden, identifying modifiable risk factors such as T2DM and clarifying their contributions to cognitive decline and dementia has become a significant research focus [14].

Current treatments for T2DM aim to achieve glycaemic control through various mechanisms, including modulation of glucose uptake, insulin sensitivity, and renal glucose excretion, and to reduce macrovascular and microvascular complications [15]. Among newer glucose-lowering drug classes, sodium–glucose cotransporter (SGLT)2 inhibitors have emerged as effective agents with well-documented cardiovascular and renal benefits in patients with T2DM [16]. Observational cohort studies and meta-analyses report that treatment with SGLT2 inhibitors is associated with a reduced incidence of dementia—including AD—compared with other antidiabetic therapies in real-world diabetic populations. Consistently, a recent meta-analysis of observational studies reported a lower pooled risk of dementia among SGLT2 inhibitor users relative to non-users or users of other glucose-lowering agents [17]. Furthermore, a meta-analysis of cohort studies evaluating the impact of SGLT2 inhibitors on dementia onset in patients with T2DM demonstrated that SGLT2 inhibitor therapy is associated with a significantly reduced risk of developing dementia, including AD, compared with other glucose-lowering treatments; however, the authors emphasized that causal inference remains limited due to the observational design of the included studies and that the underlying neuroprotective mechanisms require further elucidation [18].

Unfortunately, the neurobiological mechanisms by which SGLT2 inhibitors may affect cognitive decline or AD-related pathology are not fully understood. Findings from experimental models suggest that SGLT2 inhibition may affect various processes involved in neurodegeneration, including neuroinflammatory responses, synaptic function, and pathways involved in neuronal survival. In rodent models of DM-related cognitive impairment, treatment with SGLT2 inhibitors has been associated with improvements in cognitive behavioural status, along with reductions in neuroinflammatory mediators and oxidative stress, and regulation of BDNF signalling [19, 20].

Further evidence from pharmacological models of memory impairment suggests that canagliflozin may enhance learning and memory performance. These cognitive effects have been linked to modulation of cholinergic neurotransmission and reduction of oxidative stress, and in some *in silico* researches, have shown similar efficacy compared to established acetylcholinesterase inhibitors [21]. These findings suggest that SGLT2 inhibition may affect cognitive dysfunction through mechanisms that extend beyond classical amyloid-related pathways. In this context, experimental models that link metabolic disorders with cognitive deficits similar to those observed in AD provide an important framework for investigating the interaction between T2DM and neurodegeneration. Well-controlled animal models incorporating both metabolic and behavioural components allow the evaluation of potential therapeutic strategies under defined and reproducible conditions, and facilitate the investigation of mechanisms linking metabolic dysfunction to cognitive decline.

At the same time, currently available pharmacological treatments for AD provide only limited clinical benefit. Approved therapies range from symptomatic agents, such as acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, to more recently introduced monoclonal antibodies targeting amyloid-β; however, these interventions have shown modest effects on disease progression. Consequently, there remains considerable interest in identifying alternative or adjunctive therapeutic approaches capable of targeting broader mechanisms involved in neurodegeneration. In this regard, antidiabetic agents—particularly those with favourable metabolic and vascular profiles—have attracted attention as potential candidates for drug repurposing in the context of cognitive decline.

The present study therefore examined the effects of the non-selective SGLT inhibitor phlorizin and the selective SGLT2 inhibitor dapagliflozin in a rat model of T2DM-related cognitive dysfunction induced by high-fat diet (HFD) feeding combined with low-dose streptozotocin (STZ). The aim was to compare the effects of

these agents on metabolic disturbances and cognitive performance within the same experimental framework. Metabolic assessments of rats were monitored through blood glucose measurements, while cognitive functions were evaluated using behavioural tests; this allowed for an integrated assessment of both peripheral metabolic changes and central nervous system outcomes associated with SGLT inhibition.

2. RESULTS

2.1. Effects on Body Weight

Body weight was recorded weekly throughout the 8-week experimental period (Figure 1). An increase in body weight was observed in control animals throughout the study. In the T2DM-associated cognitive dysfunction (T2DM-CD) group, although the increase in body weight followed a different pattern compared to controls, the observed differences were not statistically significant ($p > 0.05$).

The administration of dapagliflozin, phlorizin, metformin, or rivastigmine did not lead to significant changes in body weight compared to the untreated T2DM-CD group ($p > 0.05$). Overall, these results indicate that all treatments applied in this study did not significantly affect body weight throughout the experimental period.

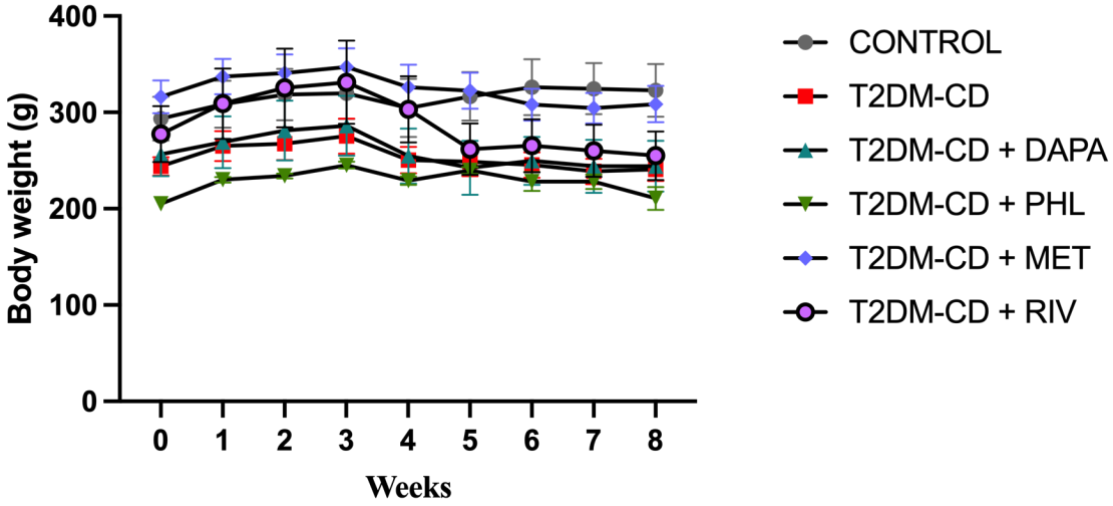


Figure 1. Body weight (g) changes during the experimental period. T2DM-CD: T2DM-related cognitive dysfunction; T2DM-CD + DAPA: dapagliflozin-treated T2DM-CD group; T2DM-CD + PHL: phlorizin-treated T2DM-CD group; T2DM-CD + MET: metformin-treated T2DM-CD group; T2DM-CD + RIV: rivastigmine-treated T2DM-CD group. Data are presented as mean ± SEM (n = 12 per group). Statistical analysis was performed using two-way ANOVA followed by Tukey's post hoc test.

2.2. Effects on Blood Glucose Levels

Blood glucose levels were monitored weekly from week 4 to week 8 after STZ administration (Figure 2). The T2DM-CD group showed significantly higher blood glucose levels compared to the control group in all measurements, confirming both successful establishment and maintenance of the diabetic state ($p < 0.01$–0.001 depending on week; Figure 2).

Dapagliflozin administration resulted in a significant reduction in blood glucose levels from week 5, and values remained significantly lower from week 5 to week 8 compared to the untreated T2DM-CD group ($p < 0.01$). Similarly, phlorizin treatment caused a reduction in blood glucose levels during the same period, with the effect becoming apparent from week 5 and continuing until week 8 ($p < 0.05$).

Metformin treatment resulted in a statistically significant reduction in blood glucose levels compared to the T2DM-CD group, particularly between weeks 6 and 8 ($p < 0.05$). In contrast, rivastigmine administration did not significantly affect blood glucose levels at any measured time point relative to the T2DM-CD group ($p > 0.05$).

Overall, temporal analysis demonstrated that SGLT inhibition produced an early and sustained improvement in glycaemic control over the 4-week treatment period, whereas metformin exerted a delayed effect and rivastigmine showed no impact on peripheral glucose regulation.

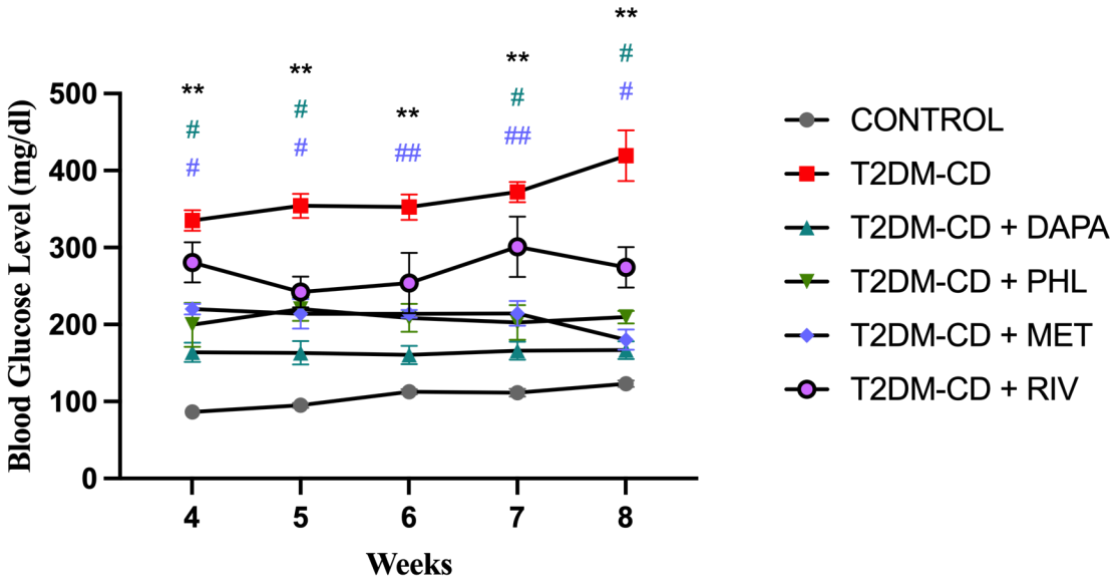


Figure 2. Blood glucose levels measured between weeks 4 and 8. T2DM-CD: T2DM-related cognitive dysfunction; T2DM-CD + DAPA: dapagliflozin-treated T2DM-CD group; T2DM-CD + PHL: phlorizin-treated T2DM-CD group; T2DM-CD + MET: metformin-treated T2DM-CD group; T2DM-CD + RIV: rivastigmine-treated T2DM-CD group. Data are presented as mean ± SEM (n = 12 per group). Statistical analysis was performed using two-way ANOVA followed by Tukey's post hoc test. * indicates comparison with the control group; # indicates comparison with the T2DM-CD group. ** $p < 0.01$ # $p < 0.05$, and ## $p < 0.01$.

2.3. Effects on Locomotor and Exploratory Activity in the Open Field Test

Locomotor activity and exploratory behaviour were evaluated using several parameters from the open field test (OFT), including latency to first entry into the center zone, duration spent in the center zone, total line crossings, rearing frequency, and grooming frequency (Figure 3).

Compared with control animals, the T2DM-CD group displayed a significantly longer latency to enter the center zone and spent less time in the center zone ($p < 0.05$ and $p < 0.01$, respectively), reflecting anxiety-like behavioural changes. Total line crossings, rearing frequency, and grooming frequency were also significantly reduced in the T2DM-CD group relative to controls ($p < 0.05$).

Treatment with dapagliflozin and phlorizin significantly improved centre-related exploratory behaviour, as evidenced by reduced latency to centre entry and increased time spent in the centre zone compared with the T2DM-CD group ($p < 0.05$ and $p < 0.01$, respectively). These treatments also partially restored total line crossings and rearing frequency ($p < 0.05$). Metformin and rivastigmine produced more limited improvements, with no consistent significant effects across all OFT parameters.

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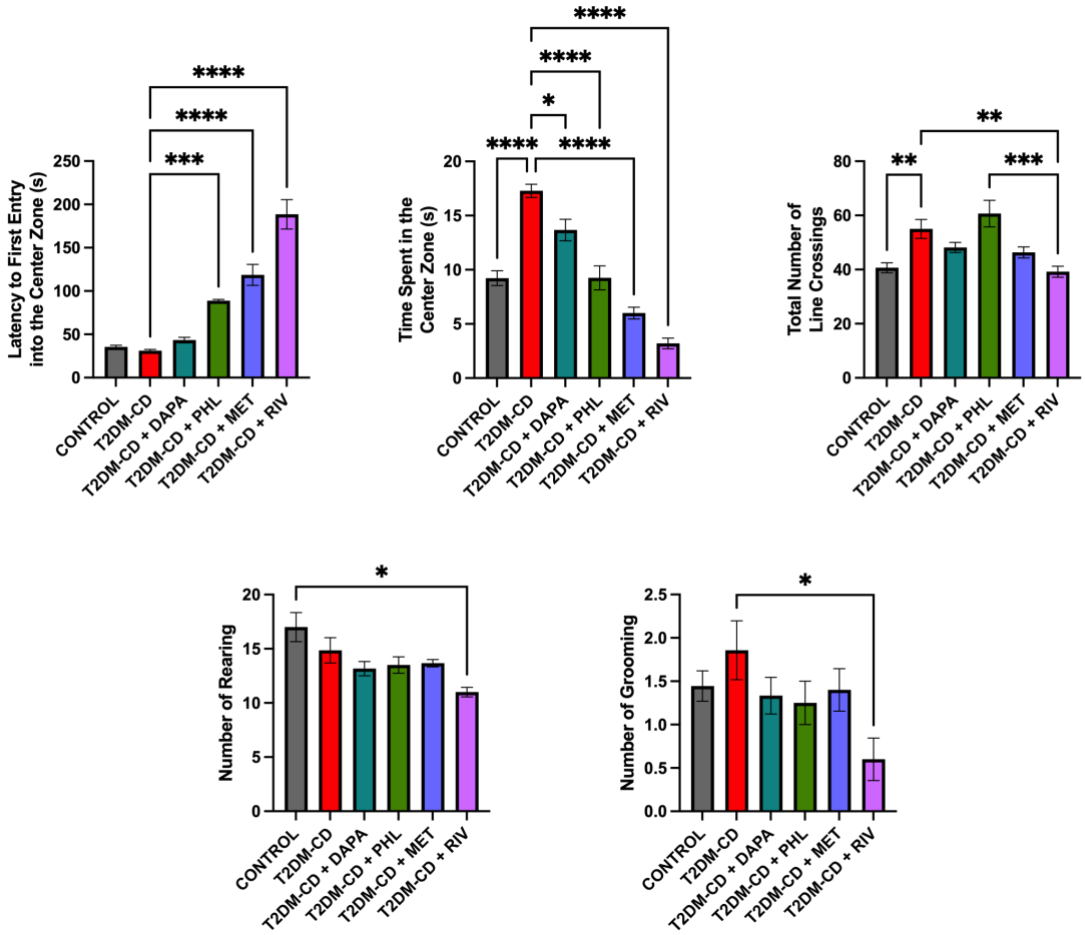


Figure 3. Open field test parameters including latency to first entry into the center zone (s), time spent in the centre zone (s), total number of lines crossed, number of rearing, and number of grooming. T2DM-CD: T2DM-related cognitive dysfunction; T2DM-CD + DAPA: dapagliflozin-treated T2DM-CD group; T2DM-CD + PHL: phlorizin-treated T2DM-CD group; T2DM-CD + MET: metformin-treated T2DM-CD group; T2DM-CD + RIV: rivastigmine-treated T2DM-CD group. Data are presented as mean ± SEM (n = 12 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.001$ among groups.

2.4. Effects on Recognition Memory in the Novel Object Recognition Test

Recognition memory performance was evaluated using the novel object recognition test (NORT) (Figure 4). Control animals demonstrated a clear preference for the novel object, as evidenced by longer exploration times and a higher preference index compared with the familiar object ($p < 0.01$). In contrast, in the T2DM-CD group, rats showed less interest in the novel object and exhibited significant deficits in recognition memory compared to the control group ($p < 0.01$).

Treatment with dapagliflozin significantly improved recognition memory, as indicated by increased exploration time of the novel object and a higher preference index compared with the T2DM-CD group ($p < 0.05$). Phlorizin treatment produced a more pronounced improvement in both parameters ($p < 0.01$). Rivastigmine also significantly enhanced recognition memory relative to the T2DM-CD group ($p < 0.05$), whereas metformin treatment resulted in a modest improvement that did not reach the magnitude observed with SGLT inhibitor treatments.

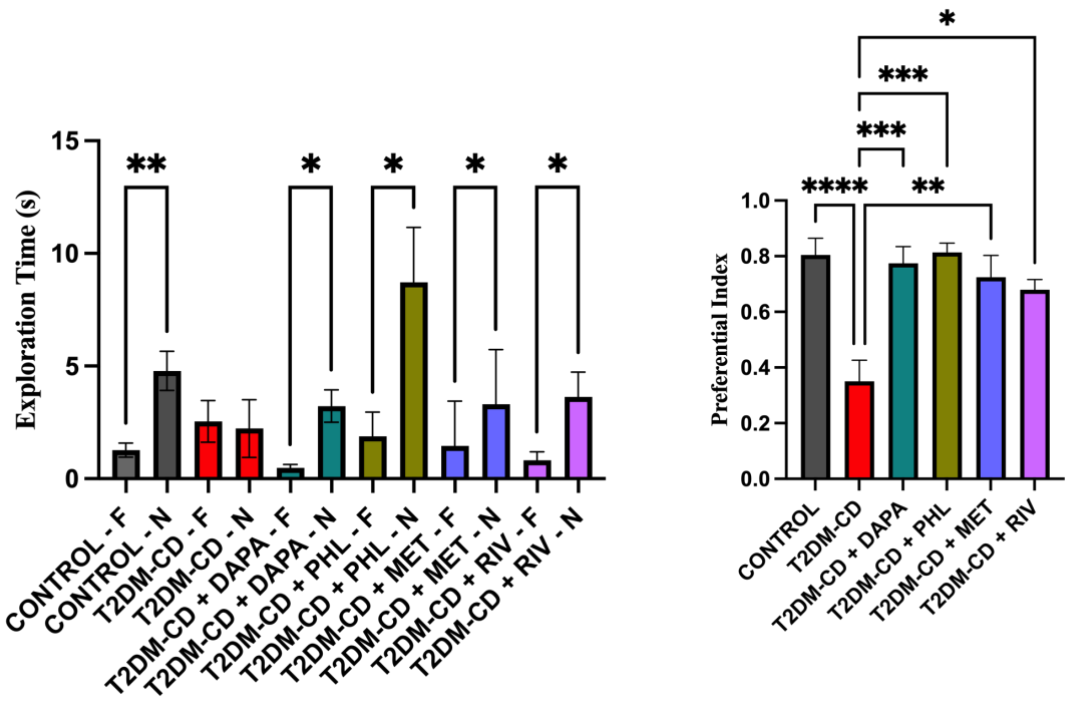


Figure 4. Novel object recognition test performance exploration time (s) and preferential index based on exploration time of the novel versus familiar object. T2DM-CD: T2DM-related cognitive dysfunction; T2DM-CD + DAPA: dapagliflozin-treated T2DM-CD group; T2DM-CD + PHL: phlorizin-treated T2DM-CD group; T2DM-CD + MET: metformin-treated T2DM-CD group; T2DM-CD + RIV: rivastigmine-treated T2DM-CD group. Data are presented as mean ± SEM (n = 12 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.001$ among groups.

3. DISCUSSION

In the present study, a HFD combined with low-dose STZ successfully induced a metabolic and cognitive phenotype consistent with T2DM-related cognitive dysfunction, as evidenced by sustained hyperglycaemia, altered body weight trajectories, and impaired recognition memory in the untreated T2DM-CD model group. This experimental approach has been widely used to investigate diabetes-related cognitive dysfunction and sporadic AD-like features in rodents [22, 23]. Importantly, the current findings extend our ongoing line of research exploring the central nervous system effects of dapagliflozin beyond its established metabolic actions. Previous experimental studies from our group have demonstrated that dapagliflozin attenuates depressive-like behaviour in the forced swim test [24], exerts anxiolytic-like effects in the open field test [25], and improves cognitive deficits in a sporadic AD rat model [26]. In this study, our findings provide further evidence that dapagliflozin, as well as the non-selective SGLT inhibitor phlorizin, may exert beneficial effects on cognitive deficits associated with T2DM. These results support that SGLT inhibition can affect central nervous system in models characterized by metabolic dysregulation and neurobehavioral changes.

During the experiment, body weight monitoring revealed a trend toward weight gain in the T2DM-CD group compared to control group, although these differences were not statistically significant. This is consistent with previous studies showing that combined HFD and STZ administration disrupts metabolic homeostasis without causing significant weight loss and closely represents human T2DM [22, 27]. Furthermore, neither treatment significantly altered body weight compared to the T2DM-CD group; this suggests that the observed cognitive outcomes are unlikely to be attributable to changes in body mass.

Blood glucose measurements confirmed hyperglycaemia in the T2DM-CD model at weeks 4 and 8, demonstrating successful T2DM induction. Both dapagliflozin and phlorizin effectively reduced blood glucose levels in accordance with their mechanisms as SGLT inhibitors that promote renal glucose excretion independently of insulin signalling [28]. Metformin also reduced glycemia in accordance with its known effects on hepatic glucose production and insulin sensitivity [29]. However, rivastigmine did not affect blood

glucose, given its role as a centrally acting cholinesterase inhibitor [30]. These findings demonstrate that SGLT inhibition in experimental animals effectively improves metabolic control in the T2DM-CD model.

According to the results from the open field test, there was no significant difference in locomotor activity between the control, T2DM-CD, and treatment groups. This result is important because it shows that neither the disease model nor the treatments caused motor changes that could affect the assessment of cognitive performance. Previous studies evaluating the cognitive effects of SGLT2 inhibitors have also reported similar findings [19, 20].

In NORT, significant deficits in recognition memory occurred in the T2DM-CD group; this is consistent with hippocampus-dependent cognitive impairments commonly observed in diabetes-related neurodegeneration [31]. Dapagliflozin treatment significantly improved novel object discrimination, while phlorizin also provided improvements. These results are consistent with other preclinical evidence suggesting that SGLT inhibition can alleviate cognitive deficits in diabetic models. Rivastigmine also improved recognition memory and demonstrated its known role in enhancing cholinergic neurotransmission and symptomatic cognitive function in AD [32]. As previously shown, metformin provided only modest cognitive benefits [33]. The more pronounced cognitive improvements observed with dapagliflozin and phlorizin suggest that SGLT inhibition may target diabetes-related cognitive dysfunction through a combination of metabolic and neurobiological mechanisms. Experimental evidence shows that SGLT2 inhibitors can reduce neuroinflammation, oxidative stress, and synaptic dysfunction in diabetic rats; these processes are closely associated with cognitive decline and AD pathology [19, 20]. In addition, SGLT inhibitors have been shown to prevent experimentally induced cognitive impairment by regulating cholinergic signalling and oxidative stress pathways; this points to a potential role of SGLT inhibition in improving non-amyloidogenic cognitive mechanisms [21]. Future research should integrate behavioural assessments with molecular markers of neuroinflammation, synaptic integrity, and cholinergic function. Furthermore, the long-term effects of SGLT inhibition on disease progression should be investigated. Such studies will be crucial in determining the therapeutic potential of SGLT inhibitors as adjunctive strategies to prevent or mitigate cognitive decline in diabetes-related neurodegenerative conditions.

4. CONCLUSION

In conclusion, this study demonstrates that both selective and non-selective SGLT inhibition markedly enhanced recognition memory in a rat model of T2DM-associated cognitive impairment, while effectively lowering blood glucose levels without affecting locomotor activity or body weight. The cognitive improvements observed with dapagliflozin and phlorizin were comparable to those seen with rivastigmine and exceeded the relatively modest effects of metformin, suggesting that SGLT inhibition may modulate cognitive function through mechanisms beyond glycaemic regulation. These findings provide experimental evidence supporting the potential of SGLT inhibitors as therapeutic candidates for diabetes-related cognitive decline and highlight the importance of future studies combining behavioural, molecular, and histopathological analyses to clarify the underlying neurobiological mechanisms.

5. MATERIALS AND METHODS

5.1. Chemicals and Reagents

Glucose, STZ, dapagliflozin, metformin, and rivastigmine were purchased from Santa Cruz Biotechnology Inc. (Dallas, TX, USA). Phlorizin was obtained from Sigma-Aldrich (St. Louis, MO, USA). (Shanghai, China). Human insulin (Humulin®) was obtained from Eli Lilly and Company.

5.2. Experimental Animals

Seventy-two adult male Sprague–Dawley rats (250–350 g) were used in this study. All experimental procedures were approved by the Marmara University Animal Experiments Local Ethics Committee (Approval no: 86.2017.mar) and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Animals were obtained from the Marmara University Experimental Animals Application and Research Center, where all experimental procedures were carried out. Rats were housed under controlled conditions (22 ± 2 °C, 60% relative humidity) with a 12 h light/12 h dark cycle and had free access to food and water throughout the study.

5.3. Experimental Design and Grouping

Rats were randomly assigned to two main groups:

Control group (n = 12): Animals were fed a standard laboratory diet for 8 weeks. At the end of the 4th week, they received an intraperitoneal injection of physiological saline (1 mL/kg) to serve as a vehicle control for STZ administration.

T2DM-related cognitive dysfunction (T2DM-CD) group (n = 60): Animals were fed a HFD containing 57% of total energy for 8 weeks. The HFD used in the study contained 45% crude fat, 20.5% crude protein, and approximately 22% carbohydrates, with additional components including crude fiber (8.8%) and ash (3.6%). The calculated metabolizable energy of the diet was 3265 kcal/kg. This composition was used to induce metabolic alterations associated with T2DM in the experimental animals. At the end of the 4th week, T2DM was induced by a single intraperitoneal injection of STZ (35 mg/kg), as previously described [22, 23].

Blood glucose levels were measured 24 hours after STZ administration. Rats with blood glucose levels >200 mg/dL were considered diabetic and included in the study. These animals were further divided into five treatment groups. All treatments were administered once daily via intragastric gavage for four consecutive weeks (weeks 4–8). Control and untreated T2DM-CD model groups received distilled water during the same period.

The experimental groups were as follows:

- **T2DM-CD group:** T2DM-induced, untreated
- **T2DM-CD + Dapagliflozin group:** T2DM-induced, 1 mg/kg/day dapagliflozin treated [19]
- **T2DM-CD + Phlorizin group:** T2DM-induced, 30 mg/kg/day phlorizin treated [34]
- **T2DM-CD + Metformin group:** T2DM-induced, 400 mg/kg/day metformin treated [35]
- **T2DM-CD + Rivastigmine group:** T2DM-induced, 2 mg/kg/day rivastigmine treated [36]

5.4. Evaluation of Diabetic Status

5.4.1. Body Weight Measurement

Body weights were recorded at baseline (week 0) and at the beginning of each experimental week throughout the 8-week study period using a calibrated digital balance.

5.4.2. Blood Glucose Measurement

Blood glucose levels were measured weekly between weeks 4 and 8. Measurements were performed without prior fasting, 30 minutes after drug administration, using tail vein blood samples analysed with a handheld glucometer (IME-DC GmbH, Hofheim, Germany). Blood glucose levels were measured 30 minutes after drug administration to assess the early pharmacodynamic response to treatment and to allow standardized comparison between groups.

5.5. Behavioural Assessment

5.5.1. Open Field Test

Locomotor activity was assessed using the OFT [37]. The device consists of an open-topped Plexiglas box measuring 50 × 50 × 40 cm, with a black floor divided into 25 equal squares (each 10 × 10 cm). It is divided into two zones: central and peripheral zones. Each rat was placed individually on the test platform and allowed to explore freely for 5 minutes. To prevent olfactory cues, the platform was cleaned with ethanol between sessions. Animal movements were recorded using a video camera. The total distance travelled (calculated as the number of frames passed), the number of rearing, the time to first reach the central zone, the total time spent in the central zone, and the number of grooming were independently assessed by two observers and used as indicators of locomotor activity.

5.5.2. Novel Object Recognition Test

The NORT was conducted to assess learning and memory based on the natural tendency of rodents to explore novel objects. The test was performed in the same Plexiglas arena under dim lighting conditions. The apparatus and objects were cleaned with ethanol between trials.

The test consisted of a habituation day and a test day.

On the habituation day, rats housed in the same cage were placed together in the empty arena for 60 minutes to acclimate to the environment.

On the test day, animals underwent two 3-minute sessions separated by a 60-minute interval. During the first session (familiarization phase), two identical (familiar) objects were placed in the arena. During the second session, one of the familiar objects was replaced with a novel object. All sessions were video-recorded.

Exploration behaviour (sniffing, touching, licking, or climbing) was scored. The ratio of time spent exploring the novel object to the familiar object was used as an indicator of recognition memory performance [38].

5.6. Termination of the Experiment

At the end of the 8-week experimental period, animals were sacrificed by decapitation at the beginning of week 9.

5.7. Statistical Analysis

All data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA). Differences among experimental groups were analysed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. Repeated measurements, including body weight and blood glucose levels, were analysed across time points within groups. A value of $p < 0.05$ was considered statistically significant.

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