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Empagliflozin reduces brain pathology in Alzheimer's disease and type 2 diabetes

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Alzheimer's disease (AD) and type 2 diabetes (T2D): More than 55 million people suffer from dementia, and it is expected that over 150 million people will suffer from this disease by 2050. AD is the most common type of dementia and while aging remains the main risk factor to suffer it, previous studies have also shown that metabolic disorders, and T2D specifically, are also major contributors (Wang et al., 2012). The prevalence of diabetes has reached 537 million people worldwide and these figures are expected to keep rising (Ahmad et al., 2022). All things considered, both diseases are a great challenge for health professionals as well as a major social problem.

Although a recent study shows different genetic susceptibility for AD and T2D (Hardy et al., 2022) previous work supports that T2D patients have an increased risk to suffer from AD, even after adjusting for cardiovascular factors (Wang et al., 2012). The involved mechanisms have not been fully elucidated; nevertheless, insulin resistance and variations in these hormone levels play a relevant role. In AD patients it has been described that insulin binding to its brain receptors is reduced, and sustained hyperglycemia over time may lead to an acceleration of brain atrophy, mediated by a decrement of neocortical insulin. Also, insulin may interfere with amyloid-beta metabolism, tau protein phosphorylation and worsen synaptotoxicity and neurodegeneration observed in AD. In addition, insulin resistance is implicated in neuroinflammation due to the release of proinflammatory cytokines, which can cross the blood-brain, increasing its permeability, impairing the endothelium of brain microvessels and changing the phenotype of astrocytes and microglia (for review De Felice, 2013).

Due to the worldwide impact of AD, searching for treatments that may delay or prevent pathological symptoms is indispensable. Acetylcholinesterase inhibitors and N-methyl-D-aspartate antagonists are the classical pharmacological approaches for AD. More recently, anti-amyloid immunotherapy, including aducanumab or lecanemab, is providing a new option, despite the raised controversies due to the costs, adverse effects, and uncertainty regarding their capacity to modify the course of the disease (Knopman et al., 2021; Liu et al., 2023). Therefore, it is still necessary to investigate other therapeutic alternatives that may reverse or slow down brain pathology and cognitive impairment in AD. Given the relationship between AD and T2D, antidiabetic treatments might provide a relevant venue at this level. At present, many antidiabetic drugs are available, including insulin and insulin analogs, metformin, sulfonylureas, thiazolidinediones, glitazones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists or insulin and insulin derivates. Given the capacity of these drugs to reduce hyperglycemia or to limit insulin resistance, the beneficial effects at the brain level have been reported for many of these drugs. Thus glucagon-like peptide-1 receptor agonists (Reich and Holscher, 2022) or intranasal insulin (Craft et al., 2012) may reduce brain pathology in AD. Importantly, modifiable risk factors for both AD and T2D should also be taken into consideration since diet and lifestyle may directly impact the development and progression of AD (Arora et al., 2023). On the other hand, sodium-glucose cotransporter type 2 inhibitors (SGLT2i), such as empagliflozin (EMP), one of the most common antidiabetic drugs prescribed to T2D patients, may also provide a new therapeutic venue. SGLT2 co-receptors are expressed in the human central nervous system and play an important role in maintaining glucose homeostasis. It has been shown that SGLT2i have a protective effect on the neurovascular unit and the blood-brain barrier, as well as in specific cell types such as pericytes, astrocytes, microglia, and oligodendrocytes. This could be mediated by a reduced expression of proinflammatory molecules like tumor necrosis factor-α or interleukin-6. In addition, some studies have described a significant improvement in brain mitochondrial function, probably because of decreased reactive oxygen species production, mitochondrial swelling, and mitochondrial membrane depolarization, supporting altogether that SGLT2i might be an option in the search of therapeutic alternatives to reduce or slow down brain complications AD (Lin et al., 2014).

Effects of EMP on the AD and diabetic brains: Previous studies have shown that EMP reduces both cardiovascular comorbidities and deaths associated with T2D (Fitchett et al., 2019). EMP treatment successfully ameliorates metabolic compromise including altered glucose and insulin levels. While the mechanism of action of SGLT2i is insulin-independent, studies on animal models of T2D have shown that EMP preserves insulin levels for longer periods, suggesting a role in maintaining β-pancreatic activity (Hierro-Bujalance et al., 2020). Likewise, the effects of SGLT2i, and EMP specifically, on the central nervous system have also been addressed. Interestingly, a recent cohort study has compared the incidence of dementia in Ontario residents aged ≥ 66 years treated with SGLT2i and dipeptidyl peptidase IV inhibitors, showing a lower risk of dementia in those on SGLT2i. They also showed that EMP treatment reduces the adjusted hazard ratio for time to incident dementia (0.78 [95% CI 0.69–0.89]), supporting an association between treatment with SGLT2i and lower dementia risk in older people with T2D (Wu et al., 2023). Following this idea, a study using a mixed murine model of AD (APP/PS1 mouse) and T2D (db/db mouse) has revealed that treatment for 22 weeks with EMP results in beneficial effects on AD pathological features. Amyloid pathology is altered in APP/PS1xdb/db mice, in which amyloid plaques are reduced while more toxic soluble species are increased. Long-term EMP treatment reduces soluble $A\beta_{40}$ levels in the cortex from AD-T2D mice (APP/PS1xdb/db), but it also reduces cortical insoluble $A\beta_{40}$ levels and amyloid plaque burden in AD mice (**Figure 1**). In line with these observations, other studies with different antidiabetic treatments have also shown a reduction in amyloid pathology that might be mediated not only by metabolic control, but also by the beneficial effects of antidiabetic drugs on oxidative stress, inflammation, or blood-brain barrier wellbeing.

On the other hand, EMP also successfully reduces tau hyperphosphorylation in diabetic mice, and similar outcomes have been observed in other models of metabolic alterations (Khan et al., 2021). Insulin resistance may affect the balance between tau kinases and phosphatases, favoring tau hyperphosphorylation. Since increased tau phosphorylation, and not necessarily overt

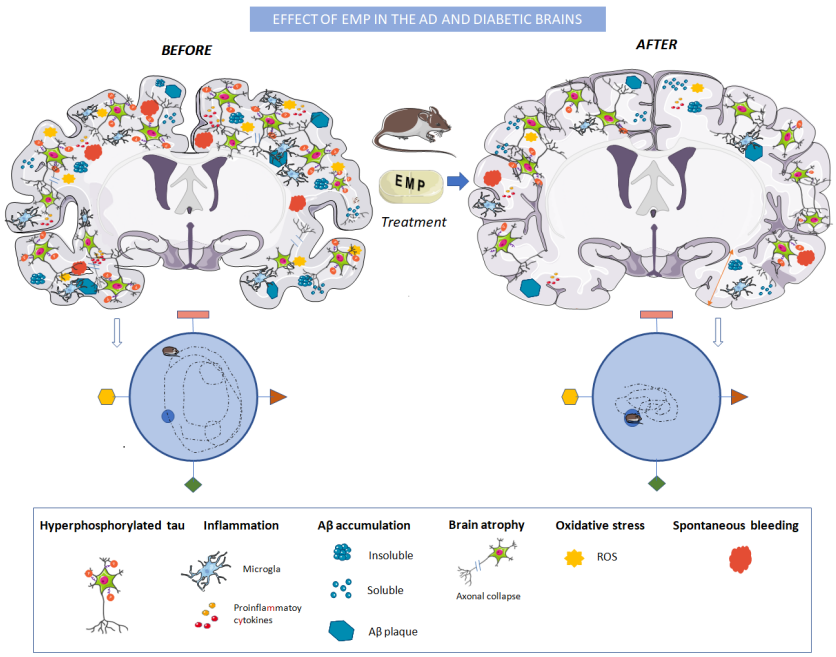

Figure 1 | **Schematic effects of empagliflozin at central level in AD and T2D mice.**
The image illustrates the schematic overview of the mouse brain with AD-T2D neuropathological characteristics and cognitive impairment. EMP treatment reduces soluble Aβ, tau hyperphosphorylation, neuronal loss and cortical thinning, microglia burden, and the presence of spontaneous hemorrhages in the cortex. In addition, EMP treatment improves learning and memory after long-term treatment. Created with SMART-Servier Medical ART. AD: Alzheimer's disease; Aβ: amyloid-beta; EMP: empagliflozin; ROS: reactive oxygen species; T2D: type 2 diabetes.

production of neurofibrillary tangles might be responsible for neuronal damage, EMP may provide a relevant opportunity at this level, supporting the beneficial effect of long-term EMP treatment in classical AD pathological features (Hierro-Bujalance et al., 2020; **Figure 1**).

Preclinical studies have also shown the neuroprotective activities of SGLT2i. EMP reduced cortical thinning and overall brain atrophy, both in T2D only (db/db) and AD-T2D (APP/PS1xdb/db) mice (Hierro-Bujalance et al., 2020). Brain atrophy was accompanied by a reduction of neurons in the proximity of amyloid plaques in AD and AD-T2D mice, and a similar profile was observed in areas far from amyloid plaques, whereas EMP successfully limited this effect. Likewise, EMP treatment reduced the percentage of degenerated neurons and apoptotic cells observed after a global ischemic-reperfusion injury in hyperglycemic rats (Amin et al., 2020). Similarly, axonal collapse is ameliorated in diabetic mice (Hayden et al., 2019), supporting its neuroprotective role at the brain level (**Figure 1**).

However, in recent years, the concept of neurodegeneration has broadened to acknowledge the relevance of other complications, including alterations of neuroregeneration processes or neuroinflammatory damage. In this sense, brain inflammation is a common complication observed in neurodegenerative diseases and lesions, as well as in T2D. Previous studies have supported the anti-inflammatory role of EMP and its capacity to reduce inflammatory mediators, including interleukin-6, interleukin-1β, and tumor necrosis factor-α, in hyperglycemic mice (Khan et al., 2021). In line with these studies, microglia burden is reduced in the proximity of cortical amyloid plaques from APP/PS1 animals treated with EMP. Likewise, microglia activation is reduced in db/db mice (Hayden et al., 2019; Hierro-Bujalance et al., 2020) and, interestingly, long-term EMP treatment successfully reduces microglia burden in areas with no plaques when APP/PS1 and APP/PS1xdb/db mice are analyzed (Hierro-Bujalance et al., 2020), supporting the anti-inflammatory role of EMP, as described for other SGT2i (**Figure 1**). Since inflammation tends to be closely related to oxidative stress, the effect of EMP at this level has also been addressed. The presence of aberrant mitochondria in the brain from db/db mice is limited by EMP (Hayden et al., 2019), and cerebral 8-hydroxy-deoxyguanosine is reduced (Lin et al., 2014). Similarly, oxidative parameters such as superoxide dismutase, catalase, or thiobarbituric acid reactive substances are counterbalanced by EMP in hyperglycaemic mice (Khan et al., 2021).

Long-term EMP treatment reduces the presence of spontaneous hemorrhages in the cortex from AD-T2D mice (Hierro-Bujalance et al., 2020) and studies on diabetic mice have shown that EMP has a beneficial effect on the neurovascular unit by limiting pericyte alterations and base membrane thickening, as well as mural endothelial cell tight and adherents junction attenuation or loss (Hayden et al., 2019). In line with these observations, other studies have shown that EMP improves endothelial cell integrity and the levels of VE-cadherin, an endothelial-specific protein crucial in maintaining endothelial integrity, after an endothelial barrier insult (Pawlos et al., 2023; **Figure 1**). These beneficial effects on different components of the neurovascular unit may underlay the observed improvements in small vessel damage and increased bleeding detected in APP/PS1xdb/db mice (Hierro-Bujalance et al., 2020).

Furthermore, it has been reported that EMP successfully prevents cognitive impairment in db/db mice (Lin et al., 2014; Hierro-Bujalance et al., 2020) and other models of metabolic alterations (Khan et al., 2021). The beneficial effects of EMP at the cognitive level are also observed in AD-T2D mice and better performances are observed when episodic and working memories are assessed (Hierro-Bujalance et al., 2020). Given the pleiotropic effects of EMP on inflammation, vascular damage, neuronal population, and Alzheimer's pathological features, cognitive enhancement cannot be unequivocally attributed to a single reason and it is feasible, that the combination of different factors is responsible for the overall improvement. Importantly, when the direct effect of EMP is specifically analyzed in AD mice (APP/PS1 animals) amyloid plaques are reduced, microglia burden is limited and neurons are preserved. Moreover, animals on long-term EMP treatment show better learning and memory performances, suggesting that EMP may have a direct effect on AD pathology, in addition to its role at the metabolic level.

Altogether EMP treatment has beneficial effects on different neuropathological features and cognitive impairment observed in AD alone, and when associated with T2D, as regularly observed in the clinic. Therefore, AD patients may possibly benefit from the metabolic and non-metabolic effects of SGLT2i, and EMP concretely. This approach may reduce or delay the evolution of the disease, laying the groundwork as a therapeutic alternative. Nevertheless, studies focused on antidiabetic drugs, as an option to treat dementia, are still needed to fully address their role at the brain level in AD patients.

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