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Sesamol: a Treatment for Diabetes-Associated Blood-Brain Barrier Dysfunction

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Abstract
Diabetes is a long-standing disease that leads to secondary complications of capillaries such as retinopathy, nephropathy and neuropathy. Emerging evidence suggests that diabetes may also affect the cerebromicrovasculature, the blood-brain barrier (BBB), and lead to changes in the brain that affect cognition and mood. Therefore, it is important to identify natural compounds that may have therapeutic benefit for reducing BBB dysfunction and improve patient quality of life. Preclinical evidence suggests that sesamol, a natural antioxidant in sesame seed oil, could have therapeutic benefit for treating BBB dysfunction during diabetes. Similarly, paroxetine, which shares a methylenedioxy moiety with sesamol shows clinical benefit for treating neuropathic pain associated with diabetes. This review emphasizes BBB dysfunction as a treatable secondary complication associated with diabetes and examines the evidence for the use of natural compounds like sesamol or existing therapies like paroxetine to help restore BBB function.

Keywords: BBB dysfunction, blood-brain barrier, cognition, diabetes, depression, paroxetine ,sesamol

Introduction

Microvascular dysfunction is a primary factor in the development and progression of disabilities most commonly associated with diabetes, including blindness, kidney failure, and peripheral neuropathies (1, 2, 3). Microangioapathy is clinically characterized by basement membrane thickening, cytoskeletal rearrangement, and increased paracellular leakage (4, 5). Extensive research has been conducted on microangiopathies in a number of tissues including kidney, peripheral nerves, retina, heart, and skeletal muscle (4, 6, 7). These studies have revealed that prolonged hyperglycemia, hypertension, dyslipidemia, insulin resistance and increased oxidative stress are important factors contributing to altered endothelial cell function (8, 9, 10).

Hyperglycemia-induced oxidative-stress mechanisms contribute to microvascular alterations of the kidney and retina. Furthermore, increased oxidative stress (11) or decreased antioxidant enzyme activity (12) directly correlates to altered cerebromicrovascular function. However, the role of hyperglycemia-induced oxidative stress with regard to cerebral microvascular dysfunction has been understudied. One possible explanation for this gap in knowledge is that vascular dysfunction in other tissues leads to observable changes that have a long-standing association with diabetes. Meanwhile, changes to central nervous system function are subtle, worsen with time. Often the symptomatic phase for clinical diagnosis of CNS disease is managed with therapies that enhance neuron function (15). Therefore, it is important to better understand microvascular changes that occur in presymptomatic phases of altered mood and cognition and to identify potential compounds that can mitigate pathological molecular changes in the cerebromicrovasculature.

The natural antioxidants in sesame seed oil show promise as being bioactive compounds that can aid to treat hyperglycemia induced altered blood-brain barrier (BBB) function. This is a brief review examining the bioactivity of sesamol for

the use of vascular-related neurological issues associated with diabetes and examining and how the selective serotonin reuptake inhibitor may have additional therapeutic uses for treating diabetes associated microvascularopathies.

Evidence for how perturbations in the blood-brain barrier affect cognition

The BBB is a dynamic, complex structure capable of rapid modulation and responsiveness to stimuli (13). The BBB is a semi-permeable membrane with unique characteristics that confer distinct properties that differentiate the BBB from peripheral capillaries including a well-defined basement membrane, presence of tight junctions, absence of fenestrations, and close apposition to other brain cell types, including pericytes, astrocytes, microglia, and neurons (14). The complex interaction between these cells is called the neurovascular unit. It has been known that intracellular signaling between these supporting cell types and the cerebral microvasculature can affect permeability of tight junctions (15). However, recent evidence suggests that diabetes modulates the function of supporting cell types such as astrocytes and microglia (16,17). These findings suggest that BBB dysfunction is a consequence of altered neurovascular unit cell-to-cell interactions. Moreover, the brain is a heterogeneous entity with different regions having specific neuronal functions and metabolic needs (15), thereby leading to alterations in BBB dysfunction that are region specific (18).

Previous findings have shown time-dependent and region specific alterations in BBB function during experimental diabetes (18). Interestingly, two of the most vulnerable regions to BBB dysfunction in this study were the hippocampus and the midbrain (18). These regions correlate to observed clinical pathologies in patients with diabetes such as alterations in cognitive function and mild depression. The clinical significance of these findings suggest that cerebromicrovascular dysfunction may be an underlying cause of secondary clinical pathologies in patients with diabetes. Small “openings” in the BBB can have a significant impact on BBB function and structure. Using magnetic resonance imaging on patients with type 2 diabetes, investigators showed increased BBB permeability to gadolinium-diethylenetriamine pentaacetic acid (DTPA). These findings suggest that openings in the BBB to a small molecule (gadolinium-DTPA; 570 Da) may play a role in the progressively worsened cognitive impairment or mild depression often seen in patients with diabetes (19).

The Blood-Brain Barrier Phenotype, Diabetes-associated BBB Dysfunction & Sesamol Treatment

A particularly novel aspect of BBB structure is the presence of tight junctions, which create a barrier to paracellular diffusion of solutes between adjacent endothelial cells (14). The tight junctions are dynamic structures, in which multiple signaling pathways and factors regulate the expression, localization, and protein-protein interactions of the tight junction (20). Studies have shown that changes in total expression and subcellular localization of the tight junction proteins have been associated with alterations in paracellular permeability (21). Changes in localization of some tight junction proteins may play an important role in communicating the state of cell–cell contacts to the nucleus and participating in regulation of growth, differentiation, and gene expression (22). Changes in regulation of tight junction proteins lead to small pertubations in the brain microvaculature and subsequent neuronal changes in neuron function (14, 23). A previous study showed that cognition was impaired in diabetic rats and that sesamol treatment alone could improve cognitive function (24) These findings suggest that insulin independent oxidative stress mechanisms contribute to impaired cognition during diabetes. Meanwhile, another study showed that sesamol restored expression of key tight junction proteins and restored blood-brain barrier function (25).

Tight junctions consist of the transmembrane proteins junctional adhesion molecule, occludin, and claudins, linked via accessory proteins including zonula occludens-1 and -2 to the actin cytoskeleton. Transmembrane proteins claudin 5 and occluden homotypically bind the adjacent endothelial cell to form the tight junction. Transmembrane proteins claudin 5 and occludens homotypically bind to form the tight junction. A previous study showed that sesamol increased the protein expression of both claudin-5 and occludin in isolated cerebromicrovessls (14,23). The BBB possesses a high electrical resistance (1500–2000 $\Omega*cm^2$), which creates both an electrical and physical barrier to maintain brain homeostasis (14). Due to the presence of tight junctions, efflux pumps and specific transport proteins, few chemical moieties can cross into the brain (14, 23). However, sesamol, but not associated metabolites, have been identified in brain tissue (26). To further support sesamol bioactivity in the brain, other preclinical studies of neurological diseases have shown that sesamol improves cognitive function (24, 27), motor abilities (28) and reduces biochemical markers of inflammation and oxidative stress in the brain (24, 27, 29, 30). The ability for sesamol to permeate the BBB could be attributed to its low molecular weight and lipophilic nature. The next section will review the anti-oxidant properties of sesamol and potential effects for reducing microvascular inflammation. A summary of he proposed protective molecular mechanisms of sesamol can be viewed in Figure 1.

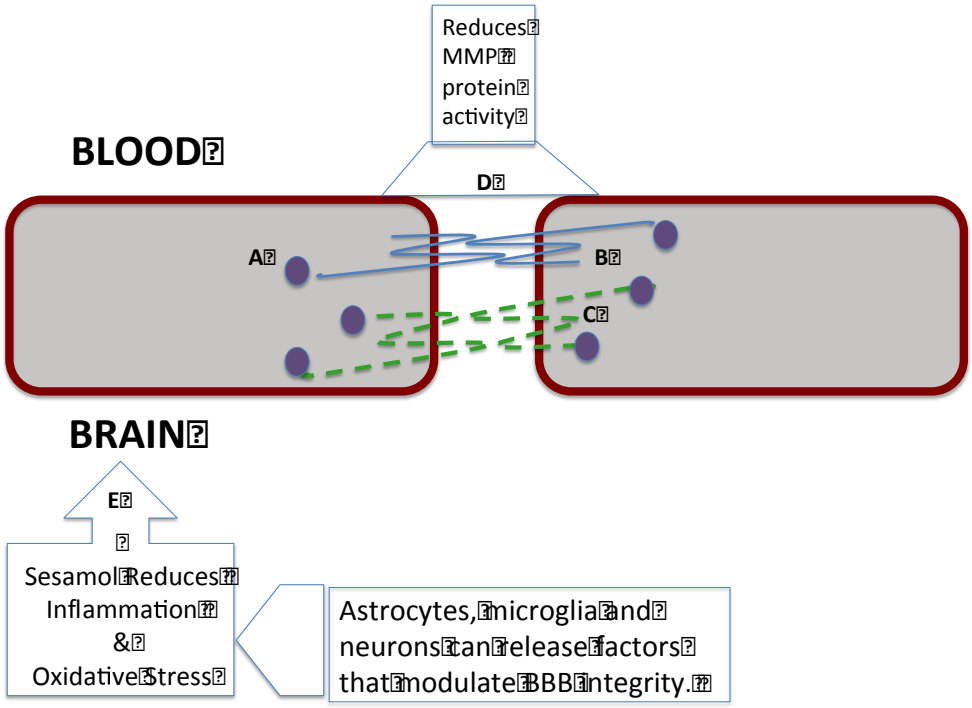

Figure 1. Schematic representation of the tight junction between two cerebral endothelial cells & potential protective effects of sesamol on BBB tight junctions. Cerebral endothelial cells also possess cadherins and junction adhesion molecule. However, the tight junction, comprised of zona occludin, claudin-5 and occludin, provides the BBB with a unique phenotype. (A) Zona occludens serve as the cytoskeletal scaffolding for the transmembrane proteins claudin-5 and occludin, which forms the cell-to-cell junction. Experimental diabetes reduces zona occludin protein expression and sesamol treatment

increases increases zona occluden protein. (B) Claudin-5 is a transmembrane protein that homotypically binds in the intracellular junction. Claudin-5 is essential for BBB tight junction formation. Sesamol increased Claudin-5 protein expression. However, reports conflict as to whether experimental diabetes decreases Claudin-5 protein. (C) Phosphorylation of occludin determines cellular location either within the cytosol (unphosphorylated) or at plasma membrane (phosphorylated) and location within the cell reflect changes in paracellular permeability. Sesamol may enhance phosphorylated occludin, thereby leading to increased BBB integrity through homotypic extracellular binding between cerebral endothelial cells. (D&E) Tight junctions are dynamic structures, which are regulated by multiple signaling pathways and external factors. External changes increasing inflammation and oxidative stress can influence tight junction protein expression and subcellular localization. (D) Tight junction proteins occluden and zona-occludin are MMP substrates. Therefore, increased MMP activity could lead to decreased tight junction protein. Sesamol can decrease MMP activity. (E) Inflammatory status of other cell types in the brain (e.g. neurons, astrocytes, microglia, etc.) can influence BBB integrity. Sesamol treatment can modulate astrocyte-mediated oxidative stress. Additionally, varying models of neurological disease show that sesamol treatment can reduce total oxidative stress and inflammatory status while enhancing antioxidant enzyme function in brain tissue.

Sesamol

Sesamol, a natural antioxidant found in sesame seed oil, is thought to have greater antioxidant activity than other antioxidant lignans found in sesame seed oil. Sesamol can scavenge superoxide anion (29, 30, 31), a property attributed to phenolic compounds. The benzodioxyl moiety gives sesamol the unique ability to neutralize hydroxyl anion (29, 30, 32) and peroxyl radical (33, 34, 35). These antioxidant properties are particularly helpful for reducing oxidative stress in lipid-rich brain vulnerable to Fenton-catalyzed lipid peroxidation due to the high metabolic activity of the brain, content of polyunsaturated fatty acids and metal cofactors. In the brain, sesamol has been shown to reduce lipid peroxidation, enhance antioxidant enzyme function and reduce markers of neuroinflammation. An *in vitro* study showed that sesamol can attenuate the production of nitric oxide (36) and hydrogen peroxide and reduces monoamine oxidase activity in cultured astrocytes (37)**,** which suggests that sesamol can modulate the activity of other cells that regulate BBB integrity. Alterations in monoamine oxidase activity correlate to oxidative stress and neurodegenerative disease development seen in aging, Alzheimer's Disease and stroke.

Additionally, the benzodioxyl group of sesamol may include gene regulating abilities, as indicated by other benzodioxyl-containing compounds (38, 39, 40). Most noteably, evidence suggests that sesamol has cardioprotective benefits by regulating vascular function and influencing circulating lipids by modulating liver function. One clinical study showed that sesame seed oil can control increased blood pressure, hyperlipidemia and lipid peroxidation (by increasing enzymatic and non-enzymatic antioxidants (41) and similar findings have been highlighted in preclinical studies (42, 43, 44). Sesamol treatment reduced plasma cholesterol and triglycerides in acute and chronic hyperlipidemia, improved vascular function (42) and can up regulate protective vascular enzymes such as peroxisome proliferator-activated receptors (43, 44) in the liver. Protective effects on the microvasculature likely stem from reduction of matrix metalloproteinase activity (43, 45, 46, 47) and stabilization of cell membranes through other redox sensitive mechanisms (48). Models of diabetic neuropathy and nephropathy highlight the combination of sesamol and insulin as the most effective mode of reducing inflammatory cytokine release (i.e. Tnf-a and TGF-B), reduced nitrosative stress and reduced caspase-3 protein

(49, 50). Decreased inflammatory cytokines and nitrosative stress have been reported in the brain with sesamol treatment (25, 27, 28). Mechanistic studies further elucidating these mechanisms within the cerebromicrovasculture are warranted. The next section will discuss the translation of findings linking sesamol to paroxetine, an approved therapy with a similar methelynedioxy moiety.

Sesamol, Paroxetine and Potential treatment for BBB dysfunction

Paroxetine is a clinically used anti-depressant classified as a selective serotonin reuptake inhibitor (SSRI). Paroxetine and sesamol both share a methlylenedioxy moiety, which is unique to paroxetine compared to other SSRIs. A cell-screening study identified paroxetine as a compound that reduced hyperglycemic endothelial cell injury by reducing mitochondrial ROS formation, mitochondrial protein oxidation and nuclear DNA damage without modulating cell bioenergetics or mitochondrial electron transport (51). At the cellular level, cross talk between NADPH oxidases and mitochondria lead to a feed-forward cycle of endothelial generation of ROS (52) during states of hyperglycemia. These findings pose an interesting concept of finding new uses for drug therapy for existing compounds outside the original indication (52). A few clinical studies report paroxetine as being useful for treating diabetes-related neuropathic pain (53, 54 , 55) or depression in patients with type 2 diabetes (57, 58, 59), while other studies point to concerns of paroxetine promoting insulin resistance alone (60, 61) or in combination with pravastatin therapy for dyslipidemia (62). Another study showed that paroxetine treatment improved insulin sensitivity in patients without diabetes (63). Additional prospective clinical studies are needed to evaluate the usefulness of paroxetine for treating BBB microangiopathy during diabetes.

Conclusion

Microvascular dysfunction leads to secondary complications associated with diabetes and surmounting evidence highlights BBB dysfunction as a potential cause of neurological effects associated with diabetes. Sesamol is a natural antioxidant in sesame seed oil that was shown to improve cognition and BBB structure and function in preclinical models of diabetes. This action is likely associated with reduced inflammatory processes in the brain and reduced peripheral cholesterol and TAGs. Sesamol and other lignans in sesame seed oil possess a methylene dioxy moiety, which is a shared chemical structure with the SSRI paroxetine. Paroxetine or sesamol maybe useful for slowing the progression of BBB dysfunction and relieve symptoms of mild cognitive deficits or depression in patients with diabetes. Clinical studies indicate that paroxetine has clinical utility for treating diabetes-associated microangiopathies like neuropathic pain and depression. However, additional studies examining the clinical utility of paroxetine for these indications and mechanistic studies investigating structure activity relationships between BBB and methylenedioxy moieties are warranted.

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