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Medical Bulletin

BLUE CROSS LIFE SCIENCES Division of Blue Cross Laboratories Pvt Ltd.

TELMISARTAN'S MULTIFACETED THERAPEUTIC HORIZON

Telmisartan, a potent angiotensin II type-1 (AT1) receptor blocker as well as partial agonist of peroxisome proliferator-activated receptor gamma (PPAR–γ), has emerged as a versatile therapeutic agent with diverse pharmacological actions beyond its primary indication for essential hypertension.

Furthermore, it has been postulated that Telmisartan possess a range of advantageous effects like anti-inflammatory, antioxidative, neuroprotection, anxiolytic and nephroprotection, shedding light on its diverse pleiotropic effects.

The below provides the multifaceted mechanisms underscoring its potential as a fundamental component in the management of conditions beyond hypertension.

I. **Neuroinflammation and Telmisartan:** Excessive renin-angiotensin system (RAS) activation, especially through AT1 receptors, contributes to brain inflammation.

- Telmisartan induces PPARγ activation (PPARγ receptors in the CNS play vital roles in neuroinflammation) independently of AT1R, preventing nuclear factor-kappa B (NFκB)-mediated inflammatory cascades. PPARγ activation leads to a dose-dependent increase in SARM (selective androgen receptor modulator) expression, a negative regulator of pro-inflammatory cytokines.
- It also reduces IL-1β-induced cyclooxygenase (COX)-2 expression, prostaglandin (PG) E2 release and reactive oxygen species (ROS) production through attenuation of COX-2 gene expression and reduction of JNK and c-Jun activation (signaling pathway involved in inflammation)

The above demonstrates a multifaceted approach to neuroprotection by modulating specific pathways associated with inflammation and oxidative stress highlighting its potential therapeutic role in neurodegenerative diseases.

II. **Telmisartan in Traumatic brain injury (TBI) and cerebral edema:** Cerebral edema, a serious complication of TBI, leads to elevated intracranial pressure and unfavorable clinical outcomes. The RAS is implicated in neuroinflammation and neurodegenerative disorders.

- Telmisartan, offers a versatile approach to managing TBI and cerebral edema. By inhibiting angiotensin II activity, it provides anti-inflammatory and neuroprotective benefits. A study confirmed the role of NOD-like receptor protein 3 (NLRP3) inflammasome-regulated IL-1β in traumatic cerebral edema. Telmisartan has shown to disrupt NLRP3 inflammasome activation, reducing IL-1β-induced inflammation. *Telmisartan thus shows promise as a therapeutic agent for TBI and cerebral edema management.*

III. **Anxiolytic effect of Telmisartan:** Emerging evidence suggests the involvement of the brain RAS in anxiety states, where angiotensin modulates neurotransmitter release.

- Telmisartan, exhibits significant anti-anxiety effects, possibly through AT1 receptor blockade in circumventricular organs and potential cerebral AT receptor blockade.

- Its anti-anxiety effects involves upregulation of angiotensin levels and receptors in the brain during anxiety, influencing neurotransmitters like noradrenaline and serotonin.
- Telmisartan's additional activities via PPAR-γ agonism and deactivation of adenine dinucleotide phosphate (NADPH) oxidase reducing oxidative stress may contribute to its role in oxidative stress management, providing added benefits.

IV. Telmisartan and Diabetes-induced vascular inflammation: Hyperglycemia triggers inflammatory responses crucial in the development of diabetic macrovascular diseases. Adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 and endothelial-leukocyte adhesion molecule-1 play a role in leukocyte adhesion, leading to vascular inflammation.

- Telmisartan reduces vascular inflammation by inhibiting the expression of inhibitory kappa B kinase beta (IKKβ) in endothelial cells. Telmisartan induces GSK3β-Ser9 [active mutant of (glycogen synthase kinase-3 beta)] phosphorylation in endothelial cells. GSK3β-Ser9 phosphorylation decreases hyperglycemia-induced NFκB p65-Ser536 phosphorylation and VCAM-1 expression and adhesion.

Through its influence on these pathways, Telmisartan can alleviate the inflammatory reactions linked to diabetes and its accompanying complications.

V. Telmisartan and Diabetic nephropathy: In diabetic nephropathy (DN), protein kinase C alpha (PKC-α) activation varies across renal structures. Increased PKC-α expression correlates with transforming growth factor beta (TGF-β1) and vascular endothelial growth factor (VEGF, a cytokine) levels, contributing to DN pathogenesis.

- Telmisartan has been found to reduce PKC-α and VEGF expression, suggesting potential nephroprotective effects through the RAS-PKC signaling cascade.
- In vitro, Telmisartan was shown to suppress ROS generation induced by high glucose levels, protecting against cellular damage.
- Preclinical studies has found it to decreases oxidative stress markers [8-hydroxydeoxyguanosin (8-OHdG), NADPH oxidase-4 (Nox4)] and improve kidney function and structure.
- It has been shown to upregulate nephrin and podocin (proteins that are both involved in the glomerular filtration barrier and the slit diaphragm, which is a key part of the filtration mechanism) signifying protective effects against DN.
- Telmisartan's dual action as a PPAR-γ agonist and AT1 receptor inhibitor contributes to renal protection.

Thus, Telmisartan exhibits multifaceted renoprotective effects suggesting its therapeutic potential in managing diabetic kidney disease.

Telmisartan's diverse pharmacological actions, including anti-inflammatory, neuroprotective, nephroprotective and anti-anxiety properties, make it a promising treatment option for a broad spectrum for various medical conditions.

Source: *Bairagi VA, et al. Future Journal of Pharmaceutical Sciences. 2024; 10:84, Song KH, et al. Biochem Biophys Res Commun. 2017; 491(4):903-911, Bakheit AH, et al. Profile Drug Subst Excip Relat Methodol. 2015; 40:371-429, Li BH, et al. Mol Biol Rep. 2015. 42:179-186*

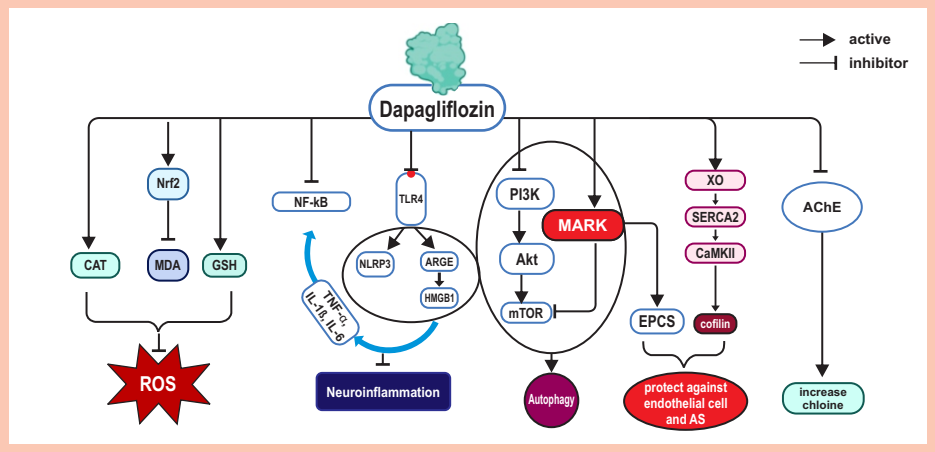
DAPAGLIFLOZIN'S FUNCTION AND MECHANISM IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD), a major type of dementia, is expected to affect 113 million people by 2050, a 2.5-fold increase from 2010. Current drugs for AD have not achieved the desired clinical efficacy due to potential risks, inapplicability, high costs, significant side effects and poor patient compliance. Studies have demonstrated the presence of sodium glucose cotransporters (SGLTs) in the mammalian nervous system, with SGLT2 being highly expressed in the hippocampus, cerebellum, and blood brain barrier (BBB) endothelial cells. Recent research suggests that sodium-glucose cotransporter 2 inhibitors (SGLT-2i) may possess neuroprotective properties, potentially paving the way for new treatments for AD.

A retrospective study found that patients with type 2 diabetes prescribed SGLT-2i had a low risk of dementia, with the lowest risk observed among those taking Dapagliflozin (DAPA). Additionally, a recent large cohort study (106,903 individuals) revealed that DAPA reduced the risk of dementia, including one of its leading causes: AD.

This provides compelling scientific evidence for the protective role of DAPA in AD.

✤ Mechanisms of DAPA in AD may comprise antioxidative stress, antineuroinflammation, upregulation of autophagy, protection of endothelial cells and acetylcholinesterase (AChE) inhibitor activity.



I. Mechanism of DAPA against oxidative stress in AD

The expression of oxidative stress products in neurodegenerative diseases is inversely proportional to the level of nuclear factor erythroid 2-related factor (Nrf2), a key oxidative stress regulator, but directly proportional to the disease's severity. As per a preclinical study, administration of DAPA plus lipopolysaccharide increased the antioxidant capacity and Nrf2 content by 1.22-fold and 98.23%, respectively which suggests that DAPA can activate the Nrf2 signalling pathway enhancing antioxidant capacity and effectively combating damage to the nervous system caused by reactive oxygen species (ROS). Another study found that, SGLT-2i decreases malondialdehyde (MDA) levels, enhances catalase (CAT) activity, and increases the content of antioxidant glutathione (GSH) in brain tissue. Therefore, DAPA plays a crucial role in AD treatment by reducing oxidative stress products associated with AD.

II. Mechanism of antineuroinflammatory action of DAPA

Toll-like receptor 4 (TLR4) overexpression in AD enhances the activity of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome, leading to diffuse neuritis and activating high-mobility group protein box 1 (HMGB1), which produces IL-1β, IL-6, and TNF-α, inhibiting microglial phagocytosis and reducing Aβ peptide clearance, thereby exacerbating AD's progression. Studies have shown that DAPA effectively reduces inflammation by

inhibiting TLR4/HMGB1 signalling and TLR4/NLRP3 inflammasome signalling. DAPA's inhibitory effect on these pathways suggests its potential as an important antineuroinflammatory agent in AD treatment.

III. Upregulation of autophagy

Under physiological conditions, the autophagy cascade is inhibited by rapamycin kinase complex 1 (mTORC1) and the activity of mTORC1 is regulated by adenylate-activated protein kinase (AMPK). The activation of AMPK during energy imbalance or nutrient deprivation can counteract the inhibitory effect of mTORC1 on autophagy. AD is accompanied by abnormal protein aggregation and the process of autophagy is closely linked to the clearance of these proteins. Function of autophagy is often inhibited in AD. Preclinical studies have shown that DAPA activates AMPK in the hippocampus and inhibits mTORC1. DAPA thereby may elevate autophagy and promote the formation of autophagosomes, thus enhancing the degradation of intracellular or extracellular aggregated proteins (including tau and Aβ deposition in AD).

IV. Protective effects on vascular endothelial cells

In patients with AD, persistent neuroinflammatory responses and oxidative stress lead to the destruction of the vascular endothelium. Impaired endothelial cells can lead to subendothelial lipid deposition, contributing to atherosclerosis (AS). This further exacerbates intracranial vascular AS and impacts not only the supply of blood flow to brain tissue but also results in neuronal damage, thus worsening the condition of AD. DAPA has been implicated in preserving endothelial cell function and preventing microvascular damage in several studies. It effectively reduces cardiac microvascular damage and endothelial dysfunction during ischemia/reperfusion by inhibiting the xanthine oxidase (XO)-sarcoplasmic reticulum Ca2+-ATPase (SERCA2)-calcium/calmodulin-dependent kinase II (CaMKII)-cofilin pathway. It inhibits inflammation and oxidative stress by activating AMPK and restores the vascular production capacity of endothelial progenitor cells. DAPA also inhibits the cell surface receptor TLR4 expression and the activation of the nuclear transcription factor, thereby reducing the release of proinflammatory mediators and further protecting endothelial cells. Thus, by improving vascular endothelial function, DAPA has the potential to be an effective drug for AD.

V. DAPA acts as a cholinesterase inhibitor

Alteration of cholinergic signalling is found mainly during early AD with the loss of cholinergic neurons in the basal nucleus and cingulate gyrus; and 90% of the basal loss occurs in the nucleus as the condition deteriorates. Reduced binding of acetylcholine (Ach) and cholinergic receptors is one of the important reasons for the emergence of psychiatric symptoms in patients with AD, therefore increasing choline levels can potentially alleviate symptoms associated with AD. A recent Mendelian randomization analysis found that SGLT-2i increased the levels of total choline and phosphatidylcholine in the blood. A preclinical study also discovered that SGLT2 inhibition could significantly reduce AChE activity and increase monoamine levels, leading to an improvement in memory dysfunction. The collective evidence suggests that DAPA may effectively increase the binding of Ach and choline receptors by inhibiting AChE activity leading to an improvement in cognitive dysfunction in patients with AD.

Thus, the preclinical data mentioned above sheds light on the role of Dapagliflozin in AD with more clinical research to comprehensively elucidate DAPA's potential for treating AD.

Source: *Chen P, et al. Medicine. 2024; 103:39, Menzies FM, et al. Nat Rev Neurosci. 2015; 16:345–57, Sa-Nguanmoo P, et al. Toxicol Appl Pharmacol. 2017; 333:43–50, Wu C-Y, et al. Diabetes Care. 2023; 46:297–304.*

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