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TELMISARTAN IN CENTRAL NERVOUS SYSTEM DISORDERS: MECHANISMS & EMERGING EVIDENCE

Telmisartan, a well-established antihypertensive drug, has shown promising therapeutic potential for a variety of central nervous system (CNS) disorders. The fundamental characteristics of telmisartan, focusing on its dual pharmacological effects as an angiotensin II type 1 receptor (AT1R) antagonist and a peroxisome proliferator-activated receptor (PPAR) γ activator, these mechanisms underpin its neuroprotective and anti-inflammatory effects, which are essential to its therapeutic benefits in CNS diseases.

Additionally the pathophysiological roles of AT1R activation beyond hemodynamic regulation, including proinflammatory responses, oxidative stress generation are mitigated by counter regulatory angiotensin II type 2 receptors (AT2Rs) mediated biological effects, opposing AT1R activation, including vasodilation, anti-inflammatory responses, and oxidative stress reduction. The cerebral RAAS constitutes an autonomous regulatory network distinct from its peripheral counterpart. Both neuronal and glial cells express complete RAAS components, including renin, Angiotensin, ACE, and specific receptors. Neuronal RAAS participates in cerebral blood flow autoregulation, neuroendocrine responses, and cognitive processing. Astrocyte-derived Ang II modulates blood-brain barrier integrity and provides neuronal metabolic support, whereas microglial RAAS activation exacerbates neuroinflammatory cascades and oxidative damage through upregulated component release.

Intercellular RAAS signaling occurs via paracrine mechanisms, with neuronal-derived angiotensins modulating adjacent cell function through AT1R/AT2R activation. This local signaling network coordinates cerebrovascular tone, synaptic plasticity, and neuronal excitability. Additionally, cerebrospinal fluid (CSF)-mediated transport enables RAAS component distribution to distant brain regions, facilitating integration with systemic cardiovascular regulation and higher-order neurological functions.

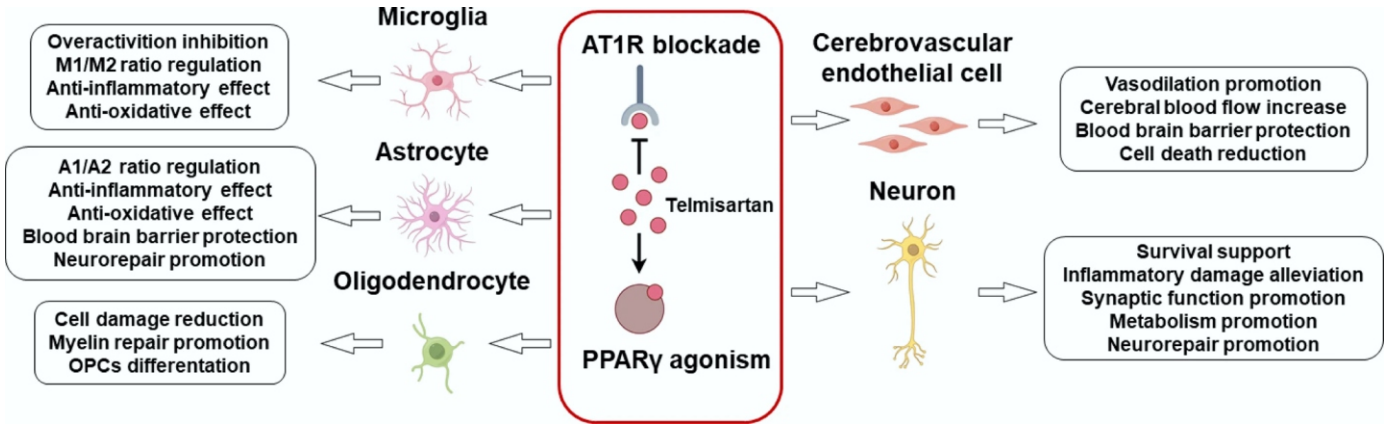
Emerging evidence implicates cerebral RAAS dysregulation in neuropathological processes, particularly through sustained neuroinflammation and redox imbalance mechanisms. These alterations demonstrate strong associations with diverse neurological disorders, highlighting the therapeutic potential of RAAS modulation. AT1R is extensively expressed in various cells within the brain, including neurons, cerebrovascular endothelial cells, astrocytes, microglia, and oligodendrocytes. Additionally, PPARγ, which is also widely expressed in the brain, is significantly linked to neuroinflammation and oxidative stress, underscoring its importance in CNS disorders.

Telmisartan modulates key cellular components of the CNS, including microglia, astrocytes, oligodendrocytes, vascular endothelial cells, and neurons, thereby offering protection against neuroinflammation, oxidative stress, and neuronal damage.

Microglia exhibit two phenotypes, M1 and M2, upon stimulation by inflammatory signals [e.g., Lipo-polysaccharides (LPS), TNF-α]. M1 microglia induce oxidative stress, secrete pro-inflammatory factors, and produce nitric oxide (NO) via iNOS, ultimately exacerbating neuronal damage. Conversely, M2 microglia secrete anti-inflammatory cytokines (e.g., IL-4, IL-10) to reduce oxidative stress and neuroinflammation, playing a protective role in the CNS. Consequently, strategies aimed at reducing the M1/M2 ratio are often deemed essential for addressing neuroinflammation.

Similarly Telmisartan has been found to mitigate the detrimental effects of reactive astrocytes on neurons, acting both directly and indirectly. It reduces the expression of A1 markers in astrocytes, downregulates the secretion of pro-inflammatory factors, and alleviates neuroinflammation and promote oligodendrocyte differentiation and maturation, and facilitate myelin formation and regeneration.

Telmisartan has been facilitating a reduction in neuronal damage by downregulating pro-inflammatory factors and iNOS expression in the brain cells.



Effects of Telmisartan on cells of the central nervous system

By targeting multiple pathways involved in the CNS disorders, telmisartan demonstrates potential as both an adjunctive and standalone therapy. Its ability to attenuate neuroinflammation and promote cellular repair highlights its versatility in CNS disease management.

Telmisartan, an AT1R antagonist with concomitant PPARγ agonistic properties, exerts anti-inflammatory and antioxidant effects in the CNS, reducing damage to the CNS and protecting cognitive functions.

Telmisartan, due to its unique ability to cross the BBB and act as a partial PPAR-γ agonist, offers a promising avenue for treating neurodegenerative & neuroinflammatory diseases such as stroke, traumatic brain injury, dementia, Parkinson's disease, demyelinating diseases, psychiatric disorders, and gliomas.

Source:*Quan W, et.al; Pharmacol Rep. 2025 Jun.*

EFFECTS OF VILDAGLIPTIN ON GLYCEMIC VARIABILITY & CORONARY PLAQUES IN IMPAIRED GLUCOSE TOLERANT PATIENTS WITH CORONARY ARTERY DISEASE

Accumulating evidence has revealed that treating dyslipidemia can reduce cardiovascular events; as such lipid-management with statins is used worldwide in the primary and secondary prevention of coronary artery disease (CAD).

It has been recently reported that glycemic variability such as postprandial hyperglycemia or hypoglycemia, which occur at an early stage of abnormal glucose tolerance, may be a significant factor aggravating the development of CAD, apart from dyslipidemia. Several studies have suggested that large glycemic variability may have stronger association with vascular injury compared with constant high blood glucose levels. Thus, the clinical effect of abnormal glucose metabolism including diabetes has been known as an important treatable target for improving CAD prognosis. The number of recent reports on the postprandial blood glucose status contributing to the development of atherosclerosis has increased; moreover, a prospective randomized controlled trial on the management of impaired glucose tolerance (IGT) has revealed that larger postprandial glucose excursion accelerates atherosclerosis formation while improving postprandial hyperglycemic state prevents atherosclerosis progression. Moreover, it has been well known that the 2-h postprandial hyperglycemic state assessed by oral glucose tolerance test (OGTT) is strongly associated with cardiovascular disease and an increased risk of death. These investigations suggest that poor management of daily glycemic variability could adversely affect the endothelial function promoting atherosclerosis progression and the advancement of plaque vulnerability, leading to fatal cardiovascular events.

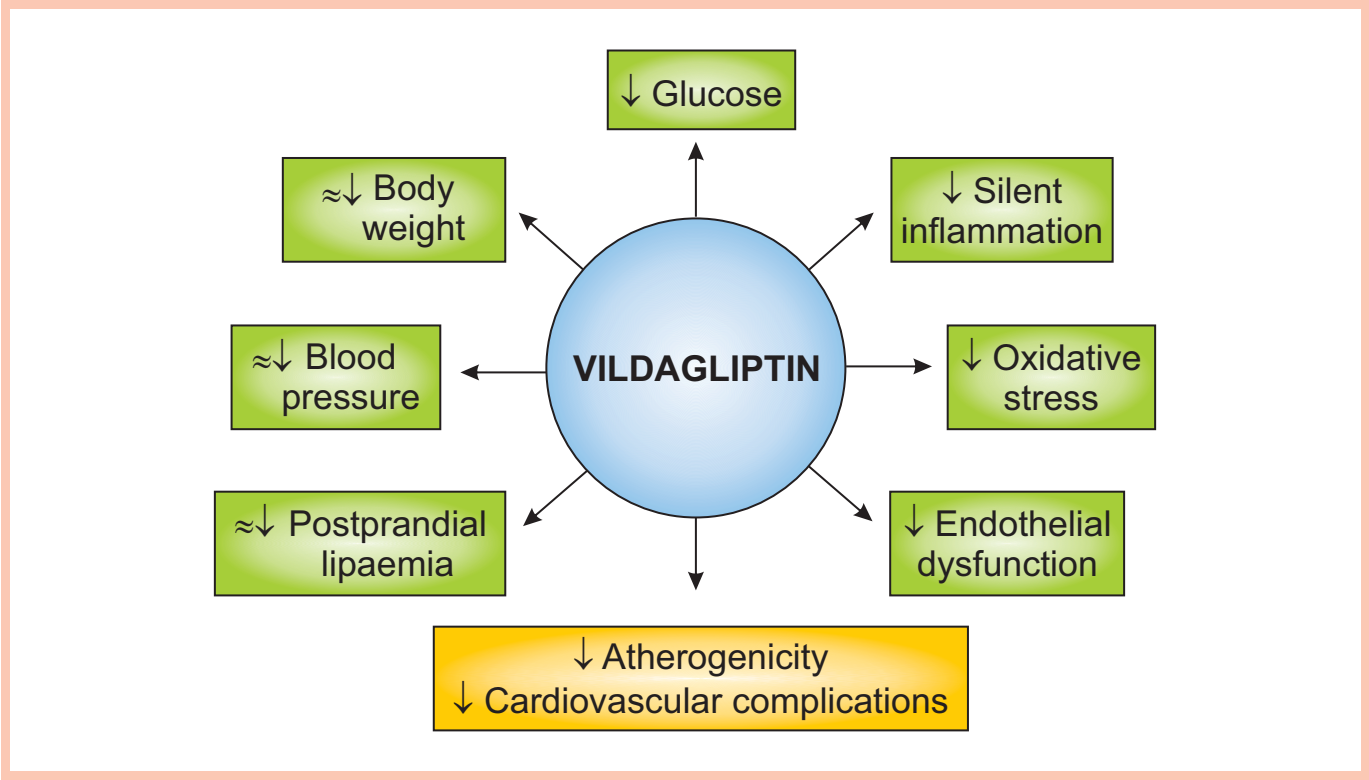
Reports of glycemic variability assessed by continuous glucose monitoring (CGM) system may impact the accelerating plaque vulnerability representing lipid-rich atheroma with thinning fibrous cap detected by optical coherence tomography (OCT), in stable lipid-controlled CAD patients.

Vildagliptin, an oral anti-hyperglycemic drug included in the class of dipeptidyl peptidase-4 (DPP-4) inhibitors, is widely used for type 2 diabetes. Several reports have showed that DPP-4 inhibitors, including vildagliptin, may present in vitro anti-atherosclerotic and cardio protective effects. Vildagliptin notably reduced the postprandial glucose spikes and hyperglycemia time without causing hypoglycemic episodes, significant decrease of Mean Amplitude of Glycemic Excursions (MAGE) and may be associated with the decreased lipid core size and increased minimum fibrous cap thickness (FCT) of the coronary plaques in CAD patients with IGT.

Additional studies elaborate on vildagliptin's plaque-stabilizing actions:

- It inhibits inflammation (e.g., NF-κB pathway, IL-1β, TNF-α) and reduces oxidative stress-both key drivers of atherosclerosis.

- It improves lipid metabolism, endothelial function, nitric oxide availability, and reduces vascular stiffness and thrombosis risk.
- Combined with metformin in CAD and diabetic patients, it lowers inflammatory cytokines (IL-1β, hsCRP), HbA1c, and supports anti-atherogenic adiponectin rise.



In stable CAD patients with IGT, addressing postprandial glucose spikes with vildagliptin may directly influence plaque vulnerability, beyond just blood sugar control. A recent clinical trial has revealed that the reduction in daily glycemic variability by vildagliptin was superior to that by sitagliptin in Japanese patients with type 2 diabetes. These findings support using Vildagliptin as part of secondary cardiovascular prevention in this subgroup, though larger and longer-term studies are needed to confirm effects on clinical outcomes like myocardial infarction or mortality.

In conclusion, vildagliptin effectively manages glucose fluctuations and shows promising effects on coronary plaque characteristics, suggesting a potential role in improving cardiovascular health in patients with diabetes or IGT.

Source: *SBMC Cardiovasc Disord . 2021 Feb 15;21:92; Cardiovasc Diabetol. 2017 May 22;16:69.*

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