# Effect of Telmisartan on Preventing Learning and Memory Deficits Via Peroxisome Proliferator-Activated Receptor-γ in Vascular Dementia Spontaneously Hypertensive Rats

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*Background:* This study aimed to explore the effect of telmisartan (TEL), as a partial peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, in vascular dementia (VaD) rats induced by middle cerebral artery occlusion (MCAO). *Methods:* Spontaneously hypertensive rats were divided into 6 groups: the sham group, model group, TEL-treated groups (1, 5, and 10 mg/kg), and TEL + GW9662 (10 mg/kg + 1 mg/kg). Using the MCAO method established the VaD rat model. Cognitive function was detected through the Morris water maze test, and matrix metalloproteinase 2 (MMP2) or matrix metalloproteinase 9 (MMP9), acetylcholinesterase (AChE), choline acetyltransferase (ChAT), and synaptophysin (SYN) in the hippocampus of rats were measured by the immunohistochemical method. *Results:* In the Morris water maze test, the spatial memory ability was significantly impaired in the model group and improved in the TEL groups (1, 5, and 10 mg/kg), but the improvement effect of TEL on spatial memory was inhibited by GW9662, a PPAR-γ antagonist. Compared with the sham group, the expression levels of MMP2, MMP9, and AChE increased and the expression levels of ChAT and SYN decreased significantly in the model group. Interestingly, TEL (1, 5, and 10 mg/kg) significantly reduced the expression levels of MMP2, MMP9, and AChE and significantly improved the expression levels of ChAT and SYN in a dose-dependent manner. However, cotreatment with GW9662 inhibited the TEL-mediated improvement effects on MMPs, the cholinergic system, and SYN. *Conclusion:* This study suggested that TEL had improvement effects in VaD rats via the PPAR-γ pathway. **Key Words:** Telmisartan—PPAR-γ—vascular dementia—cerebral ischemia.


## Introduction

Vascular dementia (VaD) is a progressive disease accompanied by cognitive decline and memory loss. Accumulating evidence indicate that cerebral ischemia contributes to neuron death and cognitive ability damage. Hypertension is an important risk factor for cerebrovascular diseases, including VaD, and long-term hypertension causes arterial stenosis and sclerosis, which cause focal cerebral ischemia and white matter lesions.[1,2] Furthermore, chronic hypertension reduces dendritic length and synaptic density, and causes neural morphological changes.[3] Therefore, the incidence of VaD was raised in hypertensive patients. Recent studies demonstrated that antihypertensive therapeutic drugs, such as telmisartan

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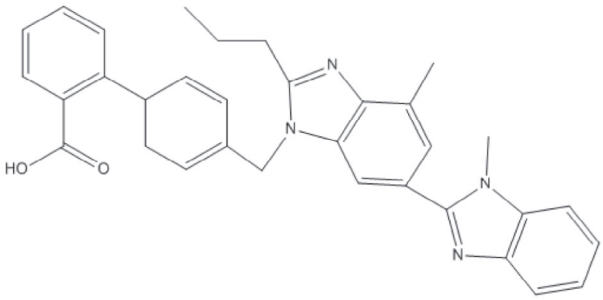


**Figure 1.** *Chemical structure of telmisartan.*

(TEL; Fig 1), could postpone the development of cognitive function impairment in hypertensive patients.[4,5] In addition, TEL had a higher liposolubility and could pass through the blood–brain barrier (BBB) and remain for a period of time in the brain.[6] Previous studies had reported that TEL had a partial peroxisome proliferator-activated receptor-γ (PPAR-γ) agonistic effect, which was considered to suppress inflammation and improve cognitive function.[7-9]

MMPs are a group of zinc-/calcium-dependent protein enzyme family mainly involved in the reorganization and reparation of the extracellular matrix and increase after cerebral ischemia. In addition, MMPs participate in the development of VaD.[10] Matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9) are the principal family members of MMPs and are implicated in BBB breakdown by attacking tight junctions, leading to leakage and hemorrhaging into brain tissue.[11] The cholinergic function plays a critical role in learning and memory deficits,[12] and acetylcholinesterase (AChE) activity significantly increases, whereas choline acetyltransferase (ChAT) activity significantly decreases, after focal cerebral ischemia–reperfusion.[13,14] However, decreasing AChE activity and increasing ChAT activity could delay cognitive decline and improve learning and memory abilities.[15,16] Synaptophysin (SYN) is a 38-kDa presynaptic vesicle-specific protein that is usually used as a presynaptic terminal specific marker to detect the density and distribution of synapses,[17] and the expression level of SYN was significantly reduced in VaD patients.[18] In the present study, we used middle cerebral artery occlusion (MCAO) models to investigate the effect of TEL on the expression level of MMPs. SYN, ChAT, and AChE were used to further explore the effect of TEL as a PPAR-γ agonist on improving cognitive decline.

## Materials and Methods

### *Animals*

Seven-week-old male spontaneously hypertensive rats (SHRs; n = 60) were supplied by the Beijing Vital River Laboratory Animal Technology Co., Ltd. (NO: 11400700107335) and placed on a basal diet. Animals were maintained for at least 7 days before the experiment in a temperature-regulated room (24°C~26°C) on a 12-hour light/dark cycle.

### *Ischemia Reperfusion Model*[19]

At the age of 8 weeks, rats were induced with transient focal ischemia by MCAO. The rats were anesthetized by 10% chloral hydrate and were fixed on the constant temperature mouse board, and their body temperatures were maintained at 36.5°C~37.5°C. A midline neck incision was made, the left common carotid artery was set out, and the common carotid artery, external carotid artery, and internal carotid artery were separated. The middle cerebral artery was occluded by the insertion of a nylon thread through the external carotid artery. When the nylon thread had come to the end of the anterior cerebral artery, the external carotid artery incision was sutured. After 2 hours of ischemia, the rats were anesthetized with ether and then gently pulled out of the nylon thread slowly until the end of the nylon thread was returned to the common carotid artery to achieve reperfusion. Sham animals received cervical surgery but without the insertion of the nylon thread.

### *Drug Preparation*

After the establishment of ischemia reperfusion model, the rats were divided into 6 groups: the sham group, model group, TEL group (1, 5, and 10 mg/kg/d), and TEL + GW9662 group (10 + 1 mg/kg/d, n = 10). The sham group and model group received daily oral doses of the same amount of normal saline, and other groups were granted the corresponding drug in the same way until the end of the experiment.

### *Behavioral Procedures*[20]

The Morris water maze test was conducted in rats after 4 weeks of treatment with or without MCAO, which included place navigation experiment and spatial probe experiment. The Morris water maze device comprises a circular stainless steel water tank that consists of 4 quadrants, and a circular hidden platform was placed in the target quadrant. Moreover, a camera was placed above the water tank to record the motion track of rats, and the environment was kept quiet and light enough.

#### Place navigation experiment

According to the northeast, northwest, southwest, and southeast quadrants, the rats facing the water tank wall were put into the water, and the escape latency was recorded in the time that the rats searched to the platform. If the time was more than 60 seconds, the escape latency was recorded as 60 seconds. The experiment was performed 2 times a day for 5 days.