Acupuncture Attenuated Vascular Dementia–Induced Hippocampal Long-Term Potentiation Impairments via Activation of D1/D5 Receptors

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Background and Purpose—Emerging evidence suggests that acupuncture could improve cognitive impairment in vascular dementia by enhancing synaptic plasticity in the hippocampus. The purpose of this study is to investigate whether dopamine, a key mediator of synaptic plasticity, is involved in this cognitive improvement.

Methods—Vascular dementia model was established by bilateral common carotid arteries occlusion in male Wistar rats. Three days after the operation, animals received acupuncture treatment for 2 weeks, once daily. The D1/D5 receptors antagonist SCH23390 was administered intraperitoneally 15 minutes before each acupuncture treatment. Morris water maze was examined after acupuncture. Long-term potentiation was studied by an electrophysiological technique. Dopamine and metabolites levels were detected by microdialysis and high-performance liquid chromatography from brain tissue. The expression of D1R and D5R was analyzed by immunofluorescence.

Results—Acupuncture remarkably reversed cognitive deficits in 2-vessel occlusion model (2VO) rats, and the acupuncture points Zusanli (ST36) and Baihui (GV20) were confirmed to be the most effective combination. Electrophysiological recording data showed that 2VO-induced impairments of long-term potentiation were prevented by acupuncture. In addition, acupuncture promoted the release of dopamine and its major metabolites in the hippocampus of 2VO rats. The immunofluorescence experiment showed that the decrease of D1R and D5R in hippocampal dentate gyrus region of 2VO rats was reversed by acupuncture. Furthermore, we found that the effects of acupuncture against 2VO-induced impairments in cognition and synaptic plasticity were abolished by SCH23390.

Conclusions—Improvement in cognition and hippocampal synaptic plasticity induced by acupuncture was achieved via activation of D1/D5 receptors in 2VO rats. (Stroke. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.014696.)

Key Words: acupuncture ■ brain ■ dopamine ■ hippocampus ■ microdialysis

Dementia, characterized by progressive cognitive decline, is associated with substantial morbidity and cost.1 Vascular dementia (VD) is not only the second most common dementia after Alzheimer disease but a potential risk factor contributing to Alzheimer disease development.2,3 Therefore, prevention and treatment of VD is important.

It is well known that the hippocampus is a key structure involved in the formation of learning and memory and is extremely sensitive to ischemic insults.4 Ischemia-induced alterations in the structure and function of neuronal circuits, including deficits in hippocampal synaptic plasticity, contribute to cognitive impairment. The dopaminergic system is a strong candidate for mediating synaptic plasticity in the hippocampus. Dopaminergic fibers arising from the ventral tegmental area and hippocampus form a functional loop which can encode different aspects of similar information into memory.5 It has been shown that the levels of neurotransmitters serotonin (5-HT), dopamine and relative metabolites 5-hydroxyindoleacetic acid (5-HTAA) and homovanillic acid (HVA) are reduced in cerebral ischemic–reperfusion mice.6 Activation of D1/D5 receptors promote the induction of hippocampal long-term potentiation (LTP), a cellular basis for memory formation.7

Acupuncture, an important traditional Chinese medicine method, is a frequently used complementary treatment in some countries to treat neurological diseases, including stroke and dementia.8,9 Our previous clinical and experimental studies provided clear evidence that acupuncture could ameliorate VD-induced learning and memory deficits.10–12

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our recent report indicated that the improvement in cognition of VD rats was achieved via the upregulation of hippocampal LTP induced by acupuncture treatment.13

Given that there are data suggesting the modulation of dopamine system on N-methyl-D-aspartate–dependent LTP, we hypothesized that acupuncture would promote the release of dopamine and activation of D1/D5R, upregulating LTP and ameliorating Vd-induced cognitive deficits.

Materials and Methods

Animals and Drugs

Two-hundred and forty male Wistar rats weighing 270 to 300 g were used in this study. All animal procedures were approved by the Experimental Ethics Committee of Capital Medical University. The D1/D5 receptors antagonist SCH23390 (Sigma-Aldrich) was dissolved in saline and was administered at 0.125 mg/kg intraperitoneally 15 minutes before each acupuncture treatment. D1/D5 receptor agonist SKF38393 (6 mg/kg, IP), 1 and 10 μmol/L dopamine, (Sigma-Aldrich) was used in our LTP experiments.

Experimental Design

Experiment I

To observe the therapeutic effect of acupuncture and to find the most effective point combinations, we performed the Morris water maze (MWM) to evaluate cognitive function. The acupuncture points applied in this study were GV20 (Baihui), ST36 (Zusanli), GV24 (Shenting), and SP10 (Xuehai). The rats were randomly divided into 6 groups: sham operated (Sham), 2-vessel occlusion model (2VO), nonacupuncture point (Non-acu+2VO), ST36+GV20, GV20+GV24, and ST36+SP10 group (n=8 per group).

Experiment II

To observe the modulation of acupuncture on hippocampal synaptic transmission, we detected LTP at the perforant pathway (PP)–dentate gyrus (DG) synapses in vivo. The rats were randomly assigned to Sham, 2VO, Non-acu+2VO, Acu+2VO, and Acu+sham groups (n=6 group).

Experiment III

To investigate whether acupuncture-induced improvement in cognition was associated with the dopaminergic system, we detected the levels of hippocampal neurotransmitters, including dopamine and dopamine metabolites by using a microdialysis technique. Then the expression of D1R and D5R in hippocampal DG region was detected using immunofluorescence. The rats were randomly assigned to Sham, 2VO, Non-acu+2VO, and Acu+2VO groups (n=6 per group).

Experiment IV

To determine whether cognitive improvement in acupuncture-treated rats is induced by activation of D1/D5R, the rats were randomly divided into 6 groups: 2VO, Acu+2VO, Acu+2VO+vehicle, Acu+2VO+SCH23390, Sham+SCH23390, and 2VO+SCH23390 (n=14 per group).

Bilateral Common Carotid Arteries Occlusion

After the rats were anesthetized with sodium pentobarbital (40 mg/kg), the VD model was established by bilateral common carotid artery occlusion (2VO). Both common carotid arteries were exposed, and then each artery was double ligated with a silk suture (5-0). In sham-operated rats, the same operation was performed except for artery occlusion.

Acupuncture Treatment

Three days after operation, animals in the acupuncture and placebo acupuncture groups received acupuncture treatment for 2 weeks, once daily, and 1 day rest after 6 treatments. Acupuncture needles (Hwato and China) with one-off sterile, 0.3×40 mm, were used to stimulate specific points and nonacupuncture points, and the location of acupuncture points in detail and operated methods are shown in Table I in the online-only Data Supplement and Figure I in the online-only Data Supplement. The sham animals received neither nonacupuncture point treatment nor active acupuncture point treatment. The rats in the sham group and 2VO group had the same procedure but without inserting needle compared with the rats in acupuncture treatment group.

MWM Test

The MWM test consists of a circular water tank 160 cm in diameter. The pool was divided into 4 quadrants. Each rat was subjected to 3 training trials per day for 5 consecutive days. It was given 90 s to search for the hidden platform. Once the rat located the submerged platform, it was allowed to remain on it for 10 s, and the latency to escape was recorded. On day 6, the probe trial was conducted by removing the platform, and the rats were permitted to swim freely for 90 s. Quadrant dwell time in the target quadrant was recorded.

Microdialysis

Rats were anesthetized with 10% chloral hydrate (0.35 mL/kg, IP) and mounted in a stereotaxic frame after the 2 weeks acupuncture treatment. The dorsal skull was exposed and implanted with vertical concentric dialysis probes (2 mm long) at the level of the hippocampus (anteroposterior±4.8; lateral=5.2; vertical=6 mm; Figure II in the online-only Data Supplement). As previously described,15 rats in vivo were perfused at a constant flow rate (1 μL/min) with artificial cerebrospinal fluid the next day after implantation. The obtained dialysate samples were transferred to a high-performance liquid chromatography system for determination of monoamine neurotransmitters and their metabolites detection as previously described.16

Immunofluorescence

Immunofluorescence imaging was performed as previously described.17 The brain tissues from rats were collected after completion of the acupuncture treatment protocol, embedded in optimal cutting temperature compound. Brain frozen tissues were sectioned with a cryostat to a thickness of 10 μm. Brain sections were blocked with donkey serum and incubated with primary antibodies to D1DR (1:100, sc-14001, Santa Cruz) and D5DR (1:100, sc-25650, Santa Cruz) at 4°C overnight. Subsequently, sections were incubated for 1 hour at room temperature in the dark with secondary antibodies. The fluorescence intensity of D1R and D5R was calculated. Images were analyzed by a researcher who was blind to the assignment group using Image-Pro Plus software.

Electrophysiological Recordings In Vivo

Because dopamine receptors exhibited higher expression in the DG than in the other hippocampal subregions,18 we tried to focus on the DG to explore the influence of acupuncture on synaptic plasticity. After acupuncture treatment, rats were anesthetized with urethane (1.2 g/kg, IP). The tip of the recording electrode was placed in granule cell layer of the DG (3.8 mm posterior to bregma, 2.2 mm lateral to the midline, and 2.8–3.1 mm ventral to dura). The stimulating electrode was inserted into the ipsilateral PP (8 mm posterior to bregma, 4.4 mm lateral to the midline, and 2.9–3.5 mm ventral to dura). The lateral PP was stimulated during the LTP experiments. After every 60 s for 30-minute stable baseline recording, a high-frequency stimulation of 4 trains of 30 stimuli at 50 Hz with 10-s intertrain interval was given to the animals. After tetanic stimulation, the field excitatory postsynaptic potential (fEPSP) was recorded at least for 60 minutes. The percentage of the ratio of absolute of fEPSP slope to baseline value was used to respectively present the fEPSP slope level.

Statistical Analysis

All data are presented as mean±SEM. Morris data, including escape latency and swimming distances, were analyzed using the 2-way
Results

Acupuncture Attenuated 2VO-Induced Learning and Memory Deficits

For the escape latency and swimming distance, there was a significant effect over time (F[4,696]=96.17, \(P<0.001\); F[4,696]=76.22, \(P<0.001\)) and also a significant effect for treatment (F[5,174]=34.88, \(P<0.001\); F[5,174]=13.07, \(P<0.001\)), but the interaction of treatment and time was not significant (F[20,696]=1.57, \(P>0.05\); F[20,696]=0.95, \(P>0.05\)). The latency to reach the hidden platform (F[5,29]=109.16, \(P<0.001\); Figure 1A) and swimming distance (F[5,29]=44.05, \(P<0.05\); Figure 1B) of the 2VO rats was longer than sham rats. After acupuncture treatment, the 2VO-induced increase in escape latency (ST36+GV20, \(P<0.01\); GV20+GV24, \(P<0.05\); ST36+SP10, \(P<0.05\); Figure 1A) and swimming distance (ST36+GV20, \(P<0.05\); GV20+GV24, \(P<0.05\); ST36+SP10, \(P<0.05\); Figure 1B) was significantly improved. There was no significant difference between the nonacupuncture group and the 2VO group in escape latency (F[5,29]=1.66, \(P>0.05\); Figure 1A) and swimming distance (F[5,29]=1.7, \(P>0.05\); Figure 1B). Acupuncture stimulation with the ST36+GV20 combination had better attenuation when compared with GV20+GV24 and ST36+SP10. No significant difference was found in swimming speed among all the groups (Figure III in the online-only Data Supplement).

In the spatial probe trials, 2VO rats spent less time in the target quadrant compared with sham rats (\(P<0.01\); Figure 1C), and acupuncture improved the reduction (\(P<0.05\); Figure 1C). There was no significant difference among the 3-point combination groups (\(P>0.05\); Figure 1C). However, the overall therapeutic effect of acupuncture stimulation with GV20+ST36 was superior over other point combinations. Thus, we used the specific point combination, GV20+ST36, throughout the later experiments. In addition, acupuncture had no significant effect on sham animals in the MWM test (Figure IV in the online-only Data Supplement).

Acupuncture Improved LTP Impairment Induced by 2VO at the PP-DG Synapse

To investigate whether acupuncture could modulate 2VO-induced inhibitory action on LTP at the PP-DG synapse, we analyzed the...
In Figure 2A, high-frequency stimulation induced a robust LTP. The fEPSP slope after high-frequency stimulation was significantly reduced compared with that in the sham group (P<0.001; Figure 2B). There was a significant difference between the acu+2VO and nonacu+2VO group (P<0.001; Figure 2B). In addition, there was no difference between the sham and acu+sham groups (P>0.05; Figure 2B).

**Acupuncture Enhanced Hippocampal Dopamine and Metabolites Levels in 2VO Rats**

To identify biological correlates of cognitive improvement in acupuncture-treated rats, levels of monoamine dopamine, dihydroxyphenylacetic acid (DOPAC), epinephrine, HVA, 5-HT, and 5-HIAA were detected by microdialysis and high-performance liquid chromatography. Compared with the sham group, the levels of dopamine (P<0.01; Figure 3A) and dopamine metabolites (DOPAC, P<0.01; Figure 3B), HVA (P<0.001; Figure 3C), and epinephrine (P<0.05; Figure 3D) in the hippocampus were significantly reduced in the 2VO group. In addition, we found that acupuncture treatment attenuated this change (dopamine, HVA, P<0.01; epinephrine, P<0.05; DOPAC, P<0.05; Figure 3A through 3D). Significant differences were observed between acu+2VO and nonacu+2VO groups (dopamine, DOPAC, HVA, P<0.05; epinephrine, P<0.01; Figure 3A through 3D). However, 5-HT and 5-HIAA levels did not differ significantly among all groups (Figure V in the online-only Data Supplement).

**Acupuncture Reversed the Reduced Expression of Dopamine Receptors in 2VO Rats**

To determine whether the dopamine 1-class receptors expression in hippocampal DG region is regulated by acupuncture, we applied immunofluorescence to analyze the expression of D1R and D5R. The expression of D1R and D5R was significantly decreased in rats after 2VO operation (D1R, P<0.001; D5R, P<0.01; Figure 4A through 4C). Acupuncture treatment significantly prevented the 2VO-induced reduction in D1/D5R (D1R, D5R, P<0.01; Figure 4A through 4C). The expression of D1R showed significant differences between acupuncture and nonacupuncture group (P<0.05; Figure 4B). But no significant difference was found for the D5R expression between acupuncture and nonacupuncture groups (P>0.05; Figure 4C). In addition, we also detected the dopamine 1-class receptors expression in hippocampal CA1 region of 2VO rats. The results were similar to that in DG (Figure VI in the online-only Data Supplement).

**D1/D5Rs Antagonists Blocked Acupuncture-Induced Cognitive Improvement**

To explore whether cognitive improvement induced by acupuncture was dependent on the activation of D1/D5Rs, we injected the D1/D5Rs antagonist SCH23390 (0.125 mg/kg, IP) in acupuncture-treated rats. For the escape latency and swimming distance, there was a significant effect over time (F[4,696]=114.6, P<0.001; F[4,696]=142.06, P<0.001) and also a significant effect for treatment (F[5,174]=45.039, P<0.001; F[5,174]=28.34, P<0.001); the interaction of treatment and time was significant (F[20,696]=2.583, P<0.001; F[20,696]=2.18, P<0.01). Application of saline in acupuncture-treated animals did not produce obvious alterations in spatial learning and memory compared with acu+2VO group (latency to escape, P>0.05; swimming distance, P>0.05; time in target quadrant, P>0.05; Figure 5A through 5C). However, administration of SCH23390 significantly prevented the acupuncture-induced therapeutic effect in 2VO rats (latency to escape, P<0.05; swimming distance, P<0.05; time in target quadrant, P<0.05; Figure 5A through 5C).

**Figure 2.** Acupuncture improved long-term potentiation (LTP) impairment induced by 2-vessel occlusion model (2VO) at the perforant pathway (PP)-dentate gyrus (DG) synapse. A, 2VO strongly inhibited the induction of LTP; and acupuncture reversed the inhibition. B, The evoked synaptic responses were summarized by calculating the average of field excitatory postsynaptic potential (fEPSP) slope 5 to 60 min after high-frequency stimulation (HFS). **P<0.001, compared as indicated.
escape, $P<0.01$; swimming distance, $P<0.05$; time in target quadrant, $P<0.05$; Figure 5A through 5C). In addition, application of SCH23390 had no significant effect on sham animals or 2VO animals in the MWM test (Figure 5A through 5C).

**D1/D5Rs Antagonists Blocked the Restoration of LTP Induced by Acupuncture**

To further confirm whether D1/D5Rs is implicated in the acupuncture-mediated restoring effect on LTP in DG, we

![Figure 3](image_url)

**Figure 3.** Acupuncture enhanced hippocampal dopamine (DA) and metabolites levels in 2-vessel occlusion model (2VO) rats. A, DA level. B, Dihydroxyphenylacetic acid (DOPAC) level. C, HVA level. D, Epinephrine (EP) level. *$P<0.05$, **$P<0.01$ and ***$P<0.001$, compared as indicated.

![Figure 4](image_url)

**Figure 4.** Acupuncture reversed the 2-vessel occlusion model (2VO)–induced reduction in dopamine receptors in dentate gyrus (DG). A, Representative photomicrographs of D1R and D5R immunofluorescence are shown for each condition. (Scale bars: 100 μm). B and C, Graphic presentations show the fluorescence intensity of D1R and D5R in the hippocampal DG region, respectively. *$P<0.05$, **$P<0.01$, and ***$P<0.001$, compared as indicated.
detected fEPSP after administration of SCH23390 or saline in acupuncture-treated rats. Application of saline in acupuncture-treated animals did not produce significant alterations in fEPSP slope level ($P > 0.05$; Figure 6A through 6B). However, administration of SCH23390 in acupuncture-treated rats significantly inhibited acupuncture-induced enhancement of hippocampal LTP ($P < 0.001$; Figure 6A through 6B). In addition, application of SCH23390 in sham animals or 2VO animals did not produce obvious alterations in the fEPSP slope ($P > 0.05$; Figure 6A through 6B).

Furthermore, we detected the fEPSP slope after dopamine direct injection into the DG of 2VO rats. The results showed that direct injection of dopamine (1 and 10 μmol/L) into the DG did not attenuate the LTP impairment (Figure VII in the online-only Data Supplement). After the dopamine D1/D5 receptor agonist SKF38393 was injected in 2VO rats, the impaired LTP was significantly improved ($P < 0.05$; Figure VII in the online-only Data Supplement).

**Discussion**

In this study, we found that acupuncture ameliorated spatial learning and memory deficits and enhanced hippocampal LTP in a VD model. The therapeutic effects may be associated with dopamine system, as manifested by increased expression of dopamine, dopamine metabolites, and dopamine receptors in the hippocampus induced by acupuncture. Moreover, the D1/D5 receptor antagonist SCH23390 significantly abolished the benefits induced by acupuncture, supporting this contention.

**Figure 5.** D1/D5Rs antagonists blocked acupuncture-induced cognitive improvement. **A**, Escape latencies. **B**, Swimming distance. **C**, The time spent in target quadrant on the sixth day. **D**, Typical swimming traces of all groups on d 5 and 6. $^*P < 0.05$, $^**P < 0.01$ vs 2-vessel occlusion model (2VO) group; $^{&&}P < 0.05$, $^{&&&}P < 0.01$ vs acu+2VO group.

**Figure 6.** D1/D5Rs antagonists blocked the restoration of long-term potentiation (LTP) induced by acupuncture. **A**, Acupuncture reversed the inhibited LTP in 2-vessel occlusion model (2VO) rats. Application of SCH23390 (0.125 mg/kg) abolished the acupuncture-induced enhancement of LTP. **B**, The evoked synaptic responses were summarized by calculating the average of field excitatory postsynaptic potential (fEPSP) slope 5 to 60 min after high-frequency stimulation (HFS). $^{***}P < 0.001$, compared as indicated.
VD is a progressive neurodegenerative disease, and the main symptom is cognition dysfunction.\textsuperscript{19} As an economic and convenient therapeutic method, acupuncture stimulation can be applied in relieving symptoms of VD.\textsuperscript{10,12} Because of the complexity of the disease, acupuncture point combination enhances the efficacy compared with single acupuncture point. Previous clinical studies selected point combination for the treatment of stroke and dementia.\textsuperscript{9,20,21} However, which point combination method is the most effective for the treatment of VD remains unclear. Our results suggest that the overall therapeutic effect of acupuncture stimulation with GV20+ST36 was superior over other points combination such as GV20+GV24 and ST36+SP10. The ST36+GV20 sites are the only combination of local and distant points among the 3 combinations we chose. So the effectiveness of ST36+GV20 might be mainly attributed to the combination of local and distant effects of the acupuncture points. Moreover, the previous studies also indicated that combination of GV20 and ST36 has a synergistically beneficial effect on the attenuation of cognitive impairment induced by brain ischemia.\textsuperscript{11,22,23}

Synaptic plasticity in the hippocampus was determined to play a key role in learning and memory processes.\textsuperscript{24} As an important functional index of synaptic plasticity, LTP is widely accepted as a molecular basis of memory formation.\textsuperscript{25} During cerebral hyperperfusion, reduction in cerebral blood flow can induce pathological alterations of neuron and dendritic spines in hippocampus, inhibiting the efficacy of synaptic transmission.\textsuperscript{26} In our study, we found that 2VO contributed to the impairment of synaptic transmission (LTP), which was ameliorated by acupuncture treatment. Our previous study also indicated that acupuncture could enhance LTP in cerebral multi-infarction rats.\textsuperscript{13}

Although several mechanisms, such as neuronal apoptosis, oxidative stress, and inflammatory responses, were considered to play a key role in cognitive impairments, recent studies on neurodegeneration have confirmed a significant involvement of neurotransmitters on cognitive changes.\textsuperscript{27,28} Accumulated evidence indicates the roles of neurotransmitters such as 5-HT, dopamine, adrenaline, acetylcholine, N-methyl-D-aspartate and their receptors in cognitive dysfunction of neurodegenerative diseases.\textsuperscript{29–31} Dopamine, one of the major neurotransmitters, is likely to modulate synaptic plasticity and plays an essential role in memory processes.\textsuperscript{32,33} Ischemia could inhibit synaptic transmission by mediating the production and storage of neurotransmitters.\textsuperscript{34} In 2VO rats, dopamine and noradrenaline levels were significantly reduced.\textsuperscript{35} In middle cerebral artery occlusion/reperfusion mice, the concentrations of dopamine and 5-HIAA were detected in hippocampus of 2VO rats, which suggested that the dopamine system, not 5-HT system, was involved in cognitive improvement and enhanced hippocampal LTP induced by acupuncture treatment.

Although dopamine is important in hippocampal synaptic plasticity, the mechanism of the dopamine effect remains unclear. A previous study indicated that D1/D5Rs play a key role in hippocampal LTP and associative learning.\textsuperscript{34} In our study, we found that the expression of D1R and D5R in the hippocampus was significantly decreased by 2VO, but acupuncture reversed the change. Furthermore, our present study also found that the therapeutic action of acupuncture on impaired cognition and hippocampal LTP in VD models could be blocked by a D1/D5 receptor antagonist SCH23390, which further provided a strong support for our conclusion that dopamine exerted its effect in cognitive improvement at least partly through the activation of D1/D5Rs. In addition, our results showed that the effect of acupuncture cannot be replaced by direct injection of dopamine into the DG. This could be partly because of the decrease of dopamine receptors in DG of 2VO rats. The dopamine D1/D5 receptor agonist SKF38393 significantly improved the impaired LTP in 2VO rats, which further illustrated the beneficial effects of D1/D5 receptor on cognitive improvement. The possible mechanisms of acupuncture on the dopaminergic system have been investigated by many studies.\textsuperscript{39–41} The vagus—adenral gland pathway,\textsuperscript{39} Nrf2-ARE (nuclear factor erythroid 2-related factor 2—antioxidant response element) signaling pathway,\textsuperscript{40} and cannabinoid receptor 1\textsuperscript{41} were all believed to be the potential mechanisms.

**Conclusions**

This study demonstrated that acupuncture treatment attenuated cerebral hyperperfusion-induced cognitive deficits and hippocampal LTP inhibition, and the attenuation was achieved by promoting dopamine and its major metabolite release and D1/D5Rs activation. The results support acupuncture as a potentially promising therapy for treatment of cognitive dysfunction in patients with VD.

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**Disclosures**

None.

**References**


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