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The positive effect of venlafaxine on central motor conduction

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ABSTRACT

Objectives: Using the triple stimulation technique (TST) and conventional transcranial magnetic stimulation (TMS), this study was designed to investigate the effect of venlafaxine on central motor conduction in healthy adults.

Patients and Methods: In this crossover, self-controlled trial, eight healthy adult volunteers were randomly divided into groups A and B. In group A, the volunteers were administered 1 venlafaxine capsule once daily for 7 consecutive days, followed by a 3-day break. Next, volunteers in this group received 1 placebo capsule once daily for 7 consecutive days. Group B received the treatments in the opposite order. The index finger tapping test, grip strength test, TST and conventional TMS examination for each hand were recorded before and one week after the administration of venlafaxine or placebo.

Results: Compared to the placebo stage, in the venlafaxine stage, the number of index finger taps was significantly increased for both hands, and the TST amplitude and area ratios were significantly increased. The improvement in the TST amplitude ratio was significantly and positively correlated with the improvements in performance on the index finger tapping test.

Conclusion: Venlafaxine positively regulates central motor conduction in healthy adults.

1. Introduction

Monoamine neurotransmitters have been shown to modulate motor performance and cerebral activation after brain injury by intervening in brain plasticity [1,2]. By regulating norepinephrine signaling, amphetamine-like agents, such as fenozolone and methylphenidate, promote the functional reorganization of the human brain with or without brain impairments [3,4]. Selective serotonin reuptake inhibitors (SSRIs) increase receptor activity and serotonergic transmission by selectively blocking the reuptake of serotonin and increasing the synaptic serotonin concentration. SSRIs activate the sensorimotor cortex and increase motion output, thus improving physical performance [5–7].

Venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), shows significant efficacy and a shorter onset time than the serotonin reuptake inhibitors. According to Zepeda et al., the early oral administration of venlafaxine provides positive neuroprotective effects on animals after stroke [8]. As shown in the functional magnetic resonance imaging (fMRI) study by Li et al. [9], venlafaxine increases excitability in the contralateral primary sensorimotor cortex, contralateral premotor cortex, and contralateral supplementary motor area of healthy adults. Xie et al. [10] proved that venlafaxine could enhance activation of the language cortices, such as the adjoining areas of posterior upper Broca area, using fMRI. In summary, venlafaxine may play an interesting and positive role in modulating brain plasticity.

However, no study has focused on examining the effects of venlafaxine using transcranial magnetic stimulation (TMS), a method that objectively quantifies conduction in the corticospinal tract [11,12]. This study aims to evaluate the positive regulatory effects of venlafaxine on central motor conduction using the triple stimulation technique (TST) and conventional TMS, thus providing evidence for the role of venlafaxine in rehabilitation after brain injury.

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2. Materials and methods

2.1. Study subjects

All subjects enrolled in this study were locally recruited healthy adult male volunteers form Chinese Han population. They met the following criteria: over 18 years old; an above middle school education; right-handedness (judged according to the Edinburgh Handedness Inventory [13]) and a willingness to provide written informed consent. Candidates who met any of the following criteria were excluded: (1) a previous history of central nervous system and non-nervous system diseases that significantly affected motor functions of the extremities, (2) any functional decompensation in other vital organs, (3) a Mini-Mental State Examination score of less than 27, (4) a Hamilton Depression Scale score of greater than 14 and a Hamilton Anxiety Scale score of greater than 7, (5) a previous history of long-term substance abuse, (6) a previous history of psychosis, (7) an allergy to venlafaxine or its components, (8) contraindications to the TMS test, and (9) an inability to cooperate during examinations. The study protocol was approved by the ethics committee of the hospital, and all selected volunteers signed the informed consent form.

2.2. Experimental design

This study utilized a randomized, double blind, placebo-controlled crossover design (Fig. 1). All subjects were randomly divided into two groups (A and B) for sequential drug administration. Group A was administered 1 venlafaxine capsule once daily (each capsule contained 75 mg of venlafaxine, Wyeth Pharmaceuticals) for 7 consecutive days, followed by a 3-day break. Next, participants in this group received 1 placebo capsule (Wyeth Pharmaceuticals) once daily for 7 consecutive days. Group B was administered 1 placebo capsule once daily for 7 consecutive days, followed by a 3-day break; and then participants in this group received 1 capsule of venlafaxine once daily for 7 consecutive days. The 7-day period of venlafaxine administration (group A $_{\text{venlafaxine administration}}$ + group B $_{\text{venlafaxine administration}}$) was defined as the venlafaxine stage, whereas the 7-day period of placebo administration (group A $_{\text{placebo administration}}$ + group B $_{\text{placebo administration}}$) was defined as the placebo stage.

Prior to drug administration and on the 7th and 18th days of the experiment, grip strength, the index finger tapping test, motor-evoked potential (MEP) induced by TST and conventional TMS measurements were recorded in each hand for every abovementioned subject to assess clinical motor function and the conduction of the central motor pathway. The blood pressure and heart rate of every subject was recorded daily, and blood samples were collected on the 7th and 18th days to assess liver function, renal function, and the blood concentration of venlafaxine. The chromatography-mass spectrometry method was used to determine the venlafaxine concentration in human plasma.

2.3. Behavioral assessment

The finger tapping test mainly measures the maximum number of taps on a computer key by the index finger within 10 s [14]. Handgrip strength was measured with a hand dynamometer in kilograms. The subject could place his arm in any position, provided that the arm or hand dynamometer did not touch the body, and the elbow could be in either flexion or extension, whichever position allowed the subject to obtain the maximum grip strength in the test.

Participants performed these experiments with each hand three continuous times in a random order, and the data were recorded and averaged. For all experiments, the consistency of the arm and hand positions was determined in each test.

2.4. Data obtained from the TST and the conventional TMS

This study used the KEYPOINT4 myoelectric potential-evoking system, a dual constant electrical stimulator (products of Dantec Dynamics A/S, Denmark), and a MAGPRO R30 magnetic stimulator (product of Medtronic, Inc., USA) to obtain the data from the TST. During the test, the subject was placed in a prone position, and the recording electrode, which was a surface electrode, was placed on the muscle belly of the first dorsal interosseus (FDI) while the muscle was in completely relaxed state. A Keypoint NET electromyogram oscilloscope was used to record the compound muscle action potential (CMAP) of the FDI scanned with the circuit, which consisted of the surface electrodes located at the muscle belly tendon.

2.4.1. TST

The TST combines TMS and peripheral stimulation with the collision technique to provide three stimuli (including one TMS and two peripheral electrical stimulations), resulting in two collisions. The peripheral nerve was electrically stimulated to measure the CMAP; CMAP was evoked by the maximum electrical stimulation in the ulnar nerve at the wrist and brachial Erb's points. The first stimulus applied over the motor cortex generated descending volleys. After a delay (delay I, the difference between the MEP latency and the M-response after wrist stimulation), a second stimulus was applied to the ulnar nerve at the wrist (electrical, supramaximal intensity). After another delay (delay II, the difference between the CMAP latency in response to the supraclavicular stimulation and the latency of the potential evoked at the wrist), a third stimulus was applied at the supraclavicular site

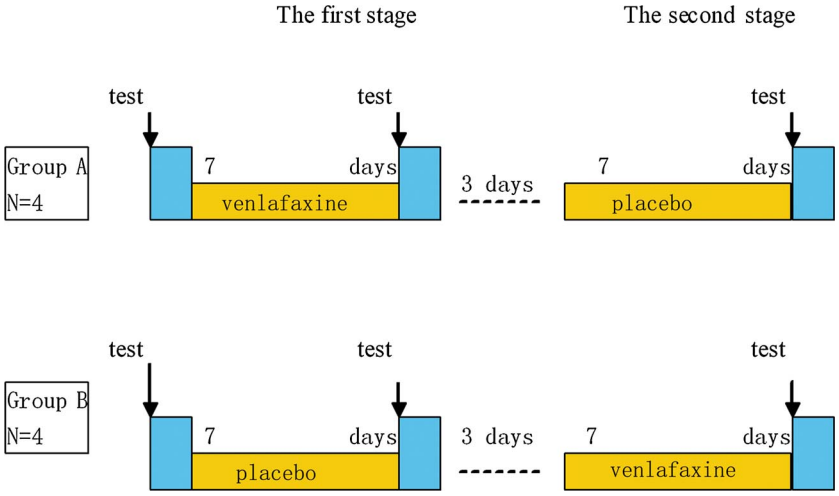

Fig. 1. A flow chart of the experimental design. A crossover design was used to compare two 7-day treatment phases with either venlafaxine or placebo. All subjects were randomly divided into two groups (A and B). The subjects in group A were administered 1 venlafaxine capsule once daily (each capsule contained 75 mg of venlafaxine, Wyeth Pharmaceuticals) for 7 consecutive days, followed by a 3-day break, and then received 1 placebo capsule once daily for 7 consecutive days. The subjects in group B were administered 1 placebo capsule once daily (Wyeth Pharmaceuticals) for 7 consecutive days, followed by a 3-day break, and then received 1 capsule of venlafaxine once daily for 7 consecutive day. Grip strength, the index finger tapping test, MEP induced by TST and conventional MEP measurements in each hand were performed for every subject at study entry and after venlafaxine and placebo administration.