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Research Report

Combined treatment with acupuncture reduces effective dose and alleviates adverse effect of L-dopa by normalizing Parkinson's disease-induced neurochemical imbalance

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ABSTRACT

This study first showed the behavioural benefits of novel combination therapy of L-dopa with acupuncture on Parkinson's disease, and its underlying mechanisms within basal ganglia. The previous study reported that acupuncture may improve the motor function of a Parkinson's disease (PD) mouse model by increasing the dopamine efflux and turnover ratio of dopamine. Hence, we hypothesised that combining L-dopa with acupuncture would have a behavioural benefit for those with PD. We performed unilateral injections of 6-OHDA into the striatum of C57Bl/6 mice to model hemi-Parkinsonian attributes. To test motor function and dyskinetic anomalies, we examined cylinder behaviour and abnormal involuntary movement (AIM), respectively. We found that (1) a 50% reduced dose of L-dopa (7.5 mg/kg) combined with acupuncture showed an improvement in motor function that was comparable to mice given the standard dose of L-dopa treatment (15 mg/kg) only, and that (2) the combination treatment (L-dopa +acupuncture) was significantly superior in reducing AIM scores when equivalent doses of L-dopa were used. The combination treatment also significantly reduces the abnormal increase of GABA contents in the substantia nigra compared to the standard L-dopa treatment. Furthermore, abnormal expres-

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sion of FosB, the immediate early gene of L-dopa induced dyskinesia (LID), was mitigated in the striatum by the combination treatment. All of these results indicate that acupuncture enhances the benefits of L-dopa on motor function with reduced dose of L-dopa and alleviating LID by normalising neurochemical imbalance within the basal ganglia.

1. Introduction

Parkinson's disease (PD) is characterised by the neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), which leads to progressive dopamine depletion in the striatum. This characteristic of PD disrupts the balance of the basal ganglia circuit and subsequently disrupts motor functions, leading to rigidity, tremor, and akinesia. One to five per cent of the older population (over 50 years of age) suffers from this second most common neurodegenerative disease (Thomas and Beal, 2007). Unfortunately, there is not yet a perfectly effective clinical treatment for PD patients; despite promising laboratory data, dopamine agonist drugs engender tolerance and adverse effects (Antonini et al., 2009). Additionally, surgeries such as deep brain stimulation and cell transplantation are costly and invasive (Fahn, 2003). A vast number of studies have been directed at making these therapies more effective and less risky.

Because it results in a dramatic improvement in motor function in the early stages of the disease, administration of the dopamine precursor L-dopa is currently one of the gold standards for PD treatment. Notwithstanding its widespread use, L-dopa produces adverse effects, including hallucination, insomnia, nausea, and dyskinesia (Fahn et al., 2004). Among these, L-dopa-induced dyskinesia (LID) is the most severe and occurs in PD patients who have received a chronic administration of L-dopa (Calabresi et al., 2010). It has been reported that more than 50% of PD patients who receive chronic L-dopa suffer from this side effect within 5 years (Rascol et al., 2000). Research continues in an effort to resolve L-dopa-related pathologies; however, much regarding these pathologies cannot yet be studied. The dose of L-dopa is still the most significant variable in the development of dyskinesia (Nyholm et al., 2010; Sharma et al., 2008), and lowering the dose of L-dopa is the best strategy for avoiding L-dopa-induced adverse effects (Cedarbaum et al., 1991; Poewe et al., 1986; Weintraub et al., 2008). However, lowering the dose of L-dopa alone is not ideal because a too-low dose, though safer, is less effective at alleviating symptoms and can even lead to extraneous disability (Kurlan, 2005). Thus, a novel treatment method that allows effective L-dopa treatment with a low dosage is highly important.

Acupuncture is one of the most common complementary therapies in East Asia, Europe and the US. Approximately 40% of PD patients in the UK use one or more complementary therapies, including acupuncture (Ferry et al., 2002). A recent clinical study also demonstrated the effectiveness of acupuncture point stimulation using bee venom or needles in treating PD patients (Cho et al., 2012). In our previous research, acupuncture improved the motor function of a PD mouse model by increasing the dopamine efflux and turnover ratio of dopamine (Kim et al., 2011a). The results showed that acupuncture enhanced dopamine transmission, leading to normalisation of the basal ganglia system.

There is growing evidence that the problems with L-dopa treatment, including adverse effects, originate from abnormal synaptic transmission (Picconi et al., 2008) and a dysregulated basal ganglia system (Bagetta et al., 2011; Kumar et al., 2009). In line with this idea, we hypothesise that combining L-dopa therapy with acupuncture could mitigate the limitations of treatment with L-dopa alone. In this study, we investigated whether this combined treatment improves motor function in 6-OHDA-induced PD mice and simultaneously alleviates LID. Furthermore, we also investigated the underlying mechanisms at the level of GABA and glutamate in the substantia nigra and FosB expression in the striatum.

2. Results

2.1. *Screening appropriate condition of L-dopa with/without acupuncture for finding most effective combination therapy*

We analysed results from the rotation test to find the effective dose of L-dopa for combination treatment with acupuncture. We performed the rotational behaviour test in a clear cylinder. Five doses of L-dopa (0, 5, 10, 15, and 20 mg/kg) with or without acupuncture treatment were administered. With the combined treatment, the dose-response curve shifted to the left compared to those treated only with L-dopa (Fig. 1A). From the curve, the dose of L-dopa needed to produce 50% of the maximum turning behaviour was found to be approximately 15 mg/kg. This dose was set as the standard. Additionally, the dosage of L-dopa that was required to produce the same turning behaviour when combined with acupuncture was 7.5 mg/kg, half of the standard L-dopa dose (Fig. 1A). Therefore, we chose two doses (7.5 and 15 mg/kg) of L-dopa to test the effectiveness of L-dopa and acupuncture combinational therapy. Moreover, in the medium dose L-dopa (10 mg/kg), acupuncture did not show LID induction. Furthermore, acupuncture showed alleviation of LID when it combined with high dose of L-dopa (20 mg/kg). Therefore, we can conclude that this motor function improvement by acupuncture is not consequent of abnormal involuntary movement (Fig. 1B).

2.2. *Synergistic effect of combined treatment on Parkinson's disease mouse model*

To find the beneficial effect of this combined treatment on PD, five main experimental treatment groups were created within 6-OHDA-induced PD mice: no-treatment, 7.5 mg/kg of L-dopa with or without acupuncture and 15 mg/kg of L-dopa with or without acupuncture. At the conclusion of the experiment, the mice were placed in a cylinder before and 2 h after L-dopa administration with or without acupuncture treatment. The 6-OHDA-depleted mice showed a significant decrease in cylinder wall touches compared to the control