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ORIGINAL ARTICLE

Neurorestorative effects of sub-chronic administration of ambroxol in rodent model of Parkinson's disease

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Abstract

Disease-modifying agents are unmet medical need for Parkinson's disease (PD). Drugs are under clinical trial to halt its progression, such as ambroxol due to its glucocerebrosidase (GCase)-stimulating activity. However, the neurorestorative effect of ambroxol is not yet investigated in any of the well-established PD models *in vivo*. Ambroxol was administered as 400 mg/kg orally twice a day from D-28 to D-70 after the unilateral intrastriatal injection of 6-hydroxydopamine (6-OHDA) in male rats. Behavioral parameters were observed every week, and at last, tyrosine hydroxylase (TH), dopamine transporter (DAT), glucocerbrosidase (GCase) enzymatic and mitochondrial complex-I activity, α-synuclein levels, and Nissl's staining were performed. Behavioral functions were progressively recovered. Ambroxol restored TH and DAT levels on D-71 as the markers of dopaminergic cell and extracellular DA concentration respectively, indicating the recovery of dopaminergic system. Factors involved in PD pathogenesis such as GCase enzymatic and mitochondrial complex-I activity were restored, and α-synuclein pathology was decreased by ambroxol. GCase deficiency is involved in mitochondrial impairment and formation of oligomeric α-synuclein aggregates which negatively affect mitochondrial function. Nissl bodies were also normalized. Therefore, both the GCase-stimulating and α-synuclein pathology-diminishing effects of ambroxol may be responsible for increment in mitochondrial function and restoration of dopaminergic system. These may act as significant mechanisms for disease-modifying potential of ambroxol. The current study provides the preclinical evidence to support the neurorestorative potential of ambroxol in 6-OHDA-induced hemiparkinson's rat model and indicates its possible use as disease-modifying agent in PD.

Keywords Ambroxol · Neurorestoration · 6-Hydroxydopamine · Parkinson's disease · Glucocerebrosidase · Disease-modifying agent

Introduction

Disease-modifying medications are unmet medical requirement in the treatment of neurodegenerative disorders (Francardo et al. 2017; Reidling et al. 2018). Disease modification may be achieved by either restraining the primary events leading to neurodegeneration, namely "neuroprotection," or upgrading the regenerative and compensatory phenomena in the related brain region; the process is defined as "neurorestoration" (Francardo et al. 2017).

Parkinson's disease (PD), one of the neurodegenerative chronic disorders, affects approximately 0.4–1% of people around 60–79 years of age and 1.9% of people more than 80 years of age worldwide (Pringsheim et al. 2014). All the marketed drugs for PD can only delay severe motor symptoms in patients and improve their overall quality of life (Pires et al. 2017). Levodopa in combination with dopamine decarboxylase inhibitor is used for symptomatic treatment of PD (Müller 2012). However, neurorestoration which can cure PD is still under investigation (Francardo et al. 2017). PD is mostly a sporadic disorder and its etiology is not completely known. However, the study of genetics, epidemiology, and neuropathology provided new insights into the underlying mechanisms of PD (Moore et al. 2005). Apart from dopamine deficit in the nigrostriatal tract α-synuclein, mitochondrial dysfunction, oxidative stress, and glucocerebrosidase (GCase) deficiency are some of the other factors reported to be involved in PD pathogenesis (Moore et al. 2005; Gegg et al. 2012).

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