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Research Report

Beneficial effects of natural phenolics on levodopa methylation and oxidative neurodegeneration ☆

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ABSTRACT

Levodopa (L-DOPA) is widely used for symptomatic management in Parkinson's disease. We recently showed that (−)-epigallocatechin-3-gallate, a tea polyphenol, not only inhibits L-DOPA methylation, but also protects against oxidative hippocampal neurodegeneration. In the present study, we sought to determine several other common dietary phenolics, namely, tea catechins [(+)-catechin and (−)-epicatechin] and a representative flavonoid (quercetin), for their ability to modulate L-DOPA methylation and to protect against oxidative hippocampal injury. A combination of *in vitro* biochemical assays, cell culture-based mechanistic analyses, and *in vivo* animal models was used. While both tea catechins and quercetin strongly inhibit human liver catechol-O-methyltransferase (COMT)-mediated O-methylation of L-DOPA *in vitro*, only (+)-catechin exerts a significant inhibition of L-DOPA methylation in both peripheral compartment and striatum in rats. The stronger *in vivo* effect of (+)-catechin on L-DOPA methylation compared to the other dietary compounds is due to its better bioavailability *in vivo*. In addition, (+)-catechin strongly reduces glutamate-induced oxidative cytotoxicity in HT22 mouse hippocampal neurons *in vitro* through inactivation of the nuclear factor-κB signaling pathway. Administration of (+)-catechin also exerts a strong neuroprotective effect in the kainic acid-induced oxidative hippocampal neurodegeneration model in rats. In conclusion, (+)-catechin is a dietary polyphenolic that may have beneficial effects in L-DOPA-based treatment of Parkinson patients by inhibiting L-DOPA methylation plus reducing oxidative neurodegeneration.

Abbreviations: L-DOPA, levodopa; PD, Parkinson disease; COMT, catechol-O-methyltransferase; 3-OMD, 3-O-methyldopa; CNS, central nervous system; H2-DCF-DA, 2′,7′-dichlorofluorescein diacetate; AdoMet, S-adenosyl-L-methionine; ROS, reactive oxygen species; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; EGCG, epigallocatechin gallate; GFAP, glial fibrillary acidic protein

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1. Introduction

The clinical symptoms of Parkinson disease (PD) are largely due to the loss of nigrostriatal dopaminergic neurons and the decrease in striatal dopamine content (Riederer and Wuketich, 1976; Da Prada et al., 1984; Huot et al., 2007). Levodopa (L-DOPA), a natural precursor for dopamine biosynthesis, is commonly used for symptom management in many PD patients. This drug is always administered together with a peripheral dopa decarboxylase inhibitor (*e.g.*, carbidopa) to reduce its rapid conversion to dopamine in peripheral tissues (Bartholini and Pletscher, 1975; Fahn, 2006). When the peripheral dopa decarboxylase is inhibited, the hepatic catechol-*O*-methyltransferase (COMT)-mediated *O*-methylation of L-DOPA becomes a major metabolic pathway. Under such conditions, the use of a COMT inhibitor (*e.g.*, tolcapone or entacapone) has been recommended for some patients, which can further improve L-DOPA bioavailability by suppressing enzymatic conversion of L-DOPA to 3-*O*-methyldopa (3-OMD) (Mannisto and Kaakkola, 1999; Heikkinen et al., 2002; Toulouse and Sullivan, 2008).

Clinical studies have shown that nearly 50% of patients using the L-DOPA+carbidopa treatment develop severe motor fluctuations (also called "wearing-off" phenomenon) and dyskinesia within the first 5 years of treatment (Koller et al., 1999; Ahlskog and Muenter, 2001; Toulouse and Sullivan, 2008). It has been suggested that some of the nervous system complications may result from a combination of the following two changes after chronic L-DOPA administration: One is the relatively large and rapid fluctuations in L-DOPA blood and CNS concentrations, and the other one is the adverse actions exerted by 3-OMD, which is a major L-DOPA metabolite formed in large quantities in both periphery and brain of patients treated with L-DOPA/carbidopa (Feuerstein et al., 1977; Raches and Fahn, 1981; Lee et al., 2008). In partial support of these suggestions, animal studies have shown that 3-OMD can interfere with L-DOPA utilization in the brain, and can also induce neuronal damage via oxidative stress (Raches and Fahn, 1981; Lee et al., 2008). Moreover, 3-OMD was found at high levels in plasma as well as cerebral spinal fluid of PD patients treated with L-DOPA/carbidopa (Sharpless et al., 1972; Tohgi et al., 1991), and its plasma levels in patients with dyskinesia were significantly higher than patients without dyskinesia (Feuerstein et al., 1977). Theoretically, addition of a COMT inhibitor to the L-DOPA/carbidopa therapy in PD patients will not only reduce L-DOPA concentration fluctuations, but will also greatly reduce 3-OMD levels, both of which would be beneficial to reducing complications. Indeed, many clinical studies have shown that such a three-drug therapy (*i.e.*, L-DOPA+carbidopa+a COMT inhibitor) improves L-DOPA bioavailability and also reduces the occurrence of adverse effects in PD patients (Müller, 2009).

We have previously shown that some of the catechol-containing bioflavonoids and tea catechins are exceptionally good substrates for human COMT (Zhu et al., 2000). In addition, bioflavonoids and tea catechins are also strong inhibitors of human COMT (Lu et al., 2003; Nagai et al., 2004; van Duursen et al., 2004; Chen et al., 2005). In our recent study, (–)-epigallocatechin-3-gallate (EGCG) was found to have beneficial effect on the L-DOPA/carbidopa therapy by inhibiting COMT-mediated L-DOPA methylation (Kang et al., 2010). In the first part of this study, therefore, we sought to further evaluate the effect of two other common tea catechins [(+)-catechin and (–)-epicatechin] and a common flavonoid (quercetin) on L-DOPA methylation to determine their relative effectiveness as naturally-occurring COMT inhibitors (Fig. 1). We found that among these dietary compounds, (+)-catechin has the strongest *in vivo* effect in modulating L-DOPA methylation in a rat model, owing to its favorable pharmacokinetic properties.

It is known that PD patients usually also suffer from a variety of non-motor symptoms including depression and dementia (Yamamoto, 2001; Padovani et al., 2006; Eskow

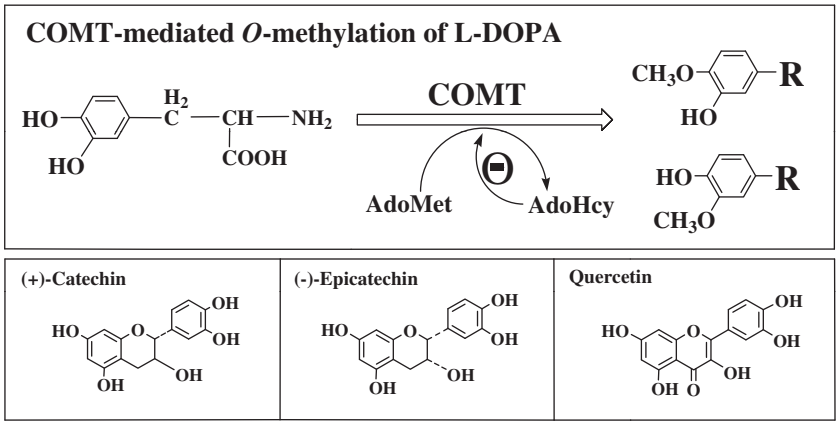

Fig. 1 – Enzymatic methylation of L-DOPA and its potential modulation by certain dietary phenolics. The upper panel shows that the COMT-catalyzed *O*-methylation of L-DOPA, which results in the formation of two mono-methylated products. It is hypothesized that certain dietary phenolics such as tea catechins and flavonoids may serve as naturally-occurring inhibitors of human COMT-mediated *O*-methylation of L-DOPA *in vivo*. The structures of (+)-catechin, (–)-epicatechin, and quercetin are shown in the lower panel. Partly owing to their strong antioxidant activity, it is also suggested that some of these dietary phenolics may have additional neuroprotective effects. The potential dual beneficial effects of certain dietary phenolics, if found to be true, would be desirable in L-DOPA-based treatment of PD patients.