Perspectives for Ginsenosides in Models of Parkinson’s Disease

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Abstract: Ginseng, the root of Panax species, is a well-known herbal medicine. It has been used as traditional medicine in Korea, China and Japan for thousands of years and now is a popular and worldwide natural medicine. The active principles of ginseng are ginsenosides which are also called ginseng saponins. Traditionally ginseng has been used primarily as a tonic to invigorate weak body functions and help the restoration of homeostasis. Current in vivo and in vitro studies demonstrate its beneficial effects in a wide range of pathological conditions such as cardiovascular diseases, cancer, immune deficiency and hepatotoxicity. Moreover, recent research indicates that some of ginseng’s active ingredients exert beneficial actions on aging and neurodegenerative disorders such as Parkinson’s disease. Essentially, antioxidant, anti-inflammatory, anti-apoptotic and immunostimulant activities are mostly underlying the postulated ginseng-mediated protective mechanisms. Next to animal studies, data from neural cell cultures contribute to the understanding of these mechanisms which involve decreasing nitric oxide, scavenging of free radicals and counteracting excitotoxicity. This paper focuses on own and other neuroprotective data on ginseng for dopaminergic neurons and intends to show aspects where neuroprotection e.g. by ginsenosides, additionally or preceding standard Parkinson therapy, could come about as a valuable contribution to slow neurodegenerative processes.

Key words: Ginsenosides, Parkinson’s disease, dopaminergic, neuroprotection

INTRODUCTION

Parkinson’s disease (PD) as a common progressive neurodegenerative disorder is characterised by massive depletion of striatal dopamine as a result of the degeneration of dopaminergic neurons in the substantia nigra. Clinically, the disease is manifested by bradykinesia, resting tremor, rigidity and disturbance of posture and gait[1]. However still to date, the etiopathogenesis of nigral dopaminergic neuron loss in PD is unclear. The presence of ongoing oxidative stress as the result of inefficacious antioxidant defence mechanisms and generation of radical oxygen species in the substantia nigra of the parkinsonian brain are important pathogenetic mechanisms[2]. It should be noted that part of these free radicals are inevitably produced by dopamine metabolism in the brain either enzymatically through the action of monoamine oxidase B or by autooxidation[3,4]. Therefore, an effective anti-parkinsonian therapy should not only alleviate the disease-associated symptoms, but should also interfere with the progressive dopaminergic death in the substantia nigra. Primary cell cultures of mesencephalic dopaminergic neurons have contributed to the understanding of molecular processes when using neurotoxic compounds that mimic cell death in PD. They also have the potential to analyse neuroprotective compounds for their ability to counteract these processes. Ginsenosides as the active ingredients in Panax ginseng are known for their anti-inflammatory, immunostimulant, antioxidative and possibly neurotrophic properties. Given their importance as a medication and health medicine their potential to dopaminergic cells in different PD cell models is analysed. However, it first it appears essential to consider the current therapeutic options and underlying theories of PD therapy to understand the need for further improvements or alternative strategies.

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Treatment of Parkinson’s disease with levodopa

Since its introduction by Birkmayer and Hornykiewicz\(^5\), levodopa remained the most effective drug for the symptomatic treatment of PD. Its effect for Parkinsonian patients is primarily based on its ability as a dopamine precursor to compensate the decrease of dopamine in the brain. Although the initial use of levodopa replacement therapy is effective in symptomatic treatment of PD, the clinical efficacy often declines after long-term therapy and additionally disabling side-effects appear, notably motor fluctuations such as the wearing-off or on-off phenomena and dyskinesia\(^9\). These motor response complications appear in most patients with advanced PD treated with levodopa. The precise mechanisms for the appearance of these treatment-related fluctuations are not clear. Nutt\(^7\) reported that the long-duration response that characterizes the first few years of levodopa use in Parkinsonian patients appears to depend on the integrity of remaining dopaminergic nerve terminals in the striatum which retain the capacity to synthesize, release, reuptake and store newly synthesized dopamine. After long-term use of levodopa and with progression of the disease, the short-duration response to levodopa and appearance of motor fluctuations are paralleled with dopaminergic degeneration and loss of release and reuptake capacity\(^8\).

Effect of levodopa on dopaminergic cells

Though dopamine replacement therapy with levodopa is successful to improve PD symptoms, it does not inhibit the progressive degeneration of dopaminergic neurons in the substantia nigra. Levodopa is not only ineffective against death of dopaminergic cells in PD patients, but there is also serious concern about possible toxic actions of levodopa to the remaining dopaminergic neurons. It has been reported that this compound is toxic to cultured dopaminergic neurons\(^9,10\). On the other hand, there is evidence indicating that large doses of levodopa do not induce dopamine neuron degeneration in mice, rats and human\(^11-13\). In PD patients, it was speculated that the remaining dopaminergic neurons in the patient’s brain could be particularly vulnerable to levodopa toxicity since they are hyperactive as a consequence of compensatory mechanisms\(^14\). In contrast, Dziewczapolski et al.\(^15\) and Murer et al.\(^16\) reported that treatment of rats with different degree of nigrostriatal damage for 6 months with oral levodopa was not toxic for remaining dopaminergic neurons. Even when levodopa administration is started during an active degenerative process of dopaminergic neurons after intrastriatal 6-hydroxydopamine (6-OHDA) injection, no aggravation of toxicity was found\(^17\).

Mechanisms underlying levodopa toxicity

It was reported that increasing oxidative stress via autooxidation of levodopa plays an important role in levodopa toxicity. Autooxidation and metabolism of levodopa can give rise to potentially harmful free radical species, hydrogen peroxide (H\(_2\)O\(_2\)) and quinones\(^18,19\). H\(_2\)O\(_2\) plays the most crucial role in the cascade of oxidative events induced by dopamine or levodopa\(^20\). Quinones were suggested to be responsible in part for the degeneration of non-dopaminergic neurons\(^21\). Their levels correlated positively with the severity of cell death in human neuroblastoma NB69 cells and the damage of dopaminergic neurons took place early before the rising of quinones. In addition to generation of H\(_2\)O\(_2\) and quinone formation, levodopa-induced cell death may result from induction of apoptosis as evidenced by the increase in caspase-3 activity in Neuro-2A cells\(^22\). Taken together, levodopa-induced toxicity is related primarily to dopamine production. Excessive dopamine metabolism by high-dose levodopa therapy may promote oxidative stress and thereby accelerate the rate of neuronal degeneration either in vivo or in vitro. Interestingly, Muriel et al.\(^23,24\) observed that levodopa treatment of control and lesioned rats with 6-OHDA altered the localization of the D\(_1\) dopamine receptor from the plasma membrane into the cytoplasm. The altered localization of D\(_1\) receptors may participate in the occurrence of the side effects of levodopa therapy such as dyskinesias and fluctuations in motor performance.

Dopamine receptors as a target in PD-therapy

Dopamine receptors belong to two classes (D1 and D2) of G protein-coupled receptors. The classification of dopamine receptors is primarily based on their effects on adenylyl cyclase activity and cAMP accumulation in the cells\(^25\). The D1 receptor subtypes promote, whereas the D2 subtypes inhibit adenylyl cyclase activity and cAMP synthesis\(^26\). It has been reported that the D2 receptors are mainly responsible for modulating the activity of voltage-sensitive Ca\(^{2+}\) and K\(^+\) channels\(^27\). Dopamine receptor agonists play an important role in anti-Parkinsonian therapy and have become increasingly popular since the introduction of bromocriptine by Calne and colleagues in 1974\(^28\). Their development aimed at reducing the unwanted motor complications produced by levodopa therapy\(^29\). Dopamine receptor agonists are being used in the initial treatment of patients with de novo PD either as