

● INVITED REVIEW

Effects of naringin, a flavanone glycoside in grapefruits and citrus fruits, on the nigrostriatal dopaminergic projection in the adult brain

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Abstract

Recently, we have demonstrated the ability of naringin, a well-known flavanone glycoside of grapefruits and citrus fruits, to prevent neurodegeneration in a neurotoxin model of Parkinson's disease. Intraperitoneal injection of naringin protected the nigrostriatal dopaminergic projection by increasing glial cell line-derived neurotrophic factor expression and decreasing the level of tumor necrosis factor-alpha in dopaminergic neurons and microglia, respectively. These results suggest that naringin can impart to the adult dopaminergic neurons the ability to produce glial cell line-derived neurotrophic factor against Parkinson's disease with anti-inflammatory effects. Based on these results, we would like to describe an important perspective on its possibility as a therapeutic agent for Parkinson's disease.

Key Words: naringin; parkinson's disease; GDNF; inflammation; mTORC1; neurodegeneration

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Naringin is a well-known flavanone glycoside of grapefruits and citrus fruits (Jagetia and Reddy, 2002). It exerts a variety of biological and pharmacological effects such as anti-inflammatory, antioxidant and lipid-lowering activities (Chanet et al., 2012). Recently, Gopinath and Sudhandiran (2012) have reported that naringin possess neuroprotective effect against neurodegenerative disorders through modulating the oxidative stress and inflammatory responses. In addition, several studies have shown that naringin has neuroprotective effects by the induction of neurotrophic factors such as brain-derived neurotrophic factor and vascular endothelial growth factor, and by the activation of anti-apoptotic pathways (Kim et al., 2009; Choi et al., 2010; Rong et al., 2012). Although these evidences suggest that naringin may be a potential natural compound involved in the prevention and treatment against neurodegenerative diseases (Jagetia and Reddy, 2005; Kim et al., 2009; Choi et al., 2010; Golechha et al., 2011; Chanet et al., 2012; Rong et al., 2012), it has not been clarified so far whether naringin has beneficial effects against degeneration of the nigrostriatal dopaminergic (DA) projection in the adult brain, which is associated with Parkinson's disease. Therefore, we have recently investigated whether daily intraperitoneal injection of naringin can have neuroprotective roles in a rat model of

1-methyl-4-phenylpyridinium (MPP⁺)-induced Parkinson's disease (Leem et al., 2014). Our results have showed that naringin treatment significantly increases glial cell line-derived neurotrophic factor (GDNF) expression and mammalian target of rapamycin complex 1 (mTORC1) activity in the nigral DA neurons, and naringin-induced production of GDNF contributes to the protection of the nigrostriatal DA projection in a neurotoxin model of Parkinson's disease (Leem et al., 2014). Moreover, naringin decreases the level of tumor necrosis factor-alpha (TNF- α) in microglia increased by MPP⁺-induced neurotoxicity. Taken together, our findings suggest that naringin may be a potential natural product to prevent degeneration of the nigrostriatal DA projection in the adult brain.

Over the last few years, there has been a growing interest in a number of pharmacological approaches to prevent and improve the neuronal dysfunction and death associated with neurodegenerative diseases. Parkinson's disease is a chronic and progressive movement disorder by the degeneration of DA neurons and biochemical reduction in striatal dopamine levels of the central nervous system, and is associated with major clinical symptoms including tremor at rest, rigidity of the limbs, slowness and paucity of voluntary movement (bradykinesia) and postural instability (a tendency to fall

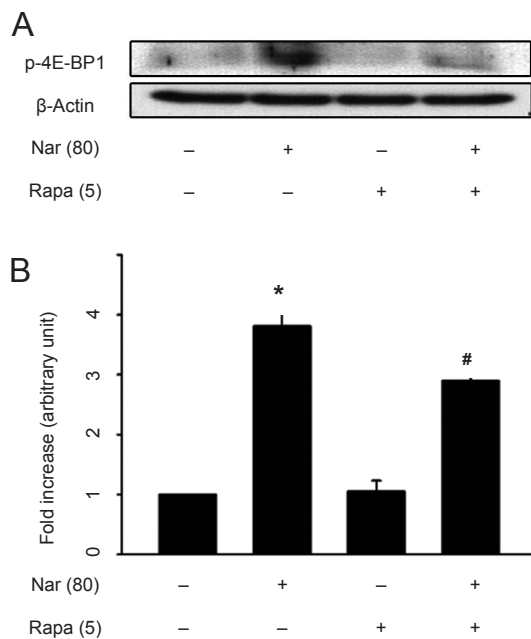


Figure 1 Western blot analysis of phospho-4E-BP1 (p-4E-BP1). To investigate the levels of p-4E-BP1, rats received daily intraperitoneal injection of rapamycin [5 mg/kg, Rapa (5)] or naringin [80 mg/kg, Nar (80)], or co-injection of rapamycin and naringin for 4 days. (A) Representative Western blots of p-4E-BP1 in the rat substantia nigra. (B) The results show that treatment with naringin induces an increase in the level of mTORC1 substrate p-4E-BP1 in the substantia nigra (**P* < 0.001, vs. intact controls), and treatment with 5 mg/kg rapamycin alone indicates no alteration on the basic level of p-4E-BP1 compared to the intact controls. However, its treatment attenuated the level of naringin-increased p-4E-BP1 [#*P* = 0.024, vs. Nar (80) alone]. All values on the optical density of each band represent mean ± SEM of three pooled samples (one-way analysis of variance and Student-Newman-Keuls analysis).

even in the absence of weakness or cerebellar balance disturbance) which are worsen over time (Savitt et al., 2006; Burke and O'Malley, 2013). It affects nearly 1% of the global population aged 65 and older (Lee and Trojanowski 2006; Recchia et al., 2008). Age-related Parkinson's disease is a complex multifactor disease, and no drugs are available to stop its progression. For several years, trophic factors have been suggested as potential therapeutic agents since they can regulate the survival of specific neuronal populations in the central nervous system (Bäckman et al., 2006). One such trophic factor is GDNF, a member of the transforming growth factor-β family of trophic factors.

GDNF is a protein that promotes the survival of many types of neurons including DA neurons (Pochon et al., 1997). The neurotrophic properties of GDNF were first described by Lin et al. (1993) who have demonstrated that GDNF promotes cell survival and increases dopamine uptake in the DA neuron cultures derived from embryonic rodent midbrain. Subsequent experiments have demonstrated that the direct injection of GDNF into the substantia nigra or striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice increases the density of DA fibers and improves motor function (Tomac et al., 1995). The neurotrophic and protective effects of GDNF were also observed in many different animal models of Parkinson's disease (Siegel

and Chauhan, 2000; Manfredsson et al., 2009; Allen et al., 2013). In addition, a conditional GDNF-null mouse showed a delayed and progressive loss of the DA neurons (Pascual et al., 2008). Although these evidences suggest that GDNF is a potent neurotrophic factor for the survival and protection of DA neurons, there is a limitation of using GDNF for Parkinson's disease patients. Since GDNF does not cross the blood-brain barrier, which is the membrane protecting the brain, direct application of GDNF to the brain is needed. Moreover, in clinical trials, intracerebroventricular injection and intraputamina infusion of GDNF did not improve parkinsonism and caused several side effects such as nausea, anorexia and vomiting (Nutt et al., 2003; Peterson and Nutt, 2008). These effects may be caused by the limited diffusion into the appropriate target sites of brain. Thus, despite the potential clinical importance of GDNF, the utilization of GDNF in clinical pharmacology and other therapeutics for Parkinson's disease will be dependent upon sustained delivery of the appropriate amount of GDNF to the target areas in a safe and efficacious manner without producing adverse effects.

Physiological responses to GDNF are mediated by a two-component receptor complex: the Ret tyrosine kinase (encoded by the c-ret proto-oncogene) and a glycosylphosphatidylinositol-linked protein called GDNF family receptor α-1 (GFRα1) (Treanor et al., 1996; Trupp et al., 1996). The binding of GDNF to Ret and GFRα1 leads to Ret phosphorylation (Kjær and Ibáñez, 2003; Sariola and Saarma, 2003), and thereby leads to the activation of several intracellular signaling pathways, including RAS/mitogen-activated protein kinase/extracellular signal-regulated kinase pathway and phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (mTOR) pathway, which in turn promotes neuronal survival and differentiation (Creedon et al., 1997; Uesaka et al., 2013).

MPP⁺ treatment decreases Akt phosphorylation in mice, which results in loss of mTORC1 activation, and a loss of Akt phosphorylation is also observed in the substantia nigra of Parkinson's disease patients (Selvaraj et al., 2012). Moreover, the activation of mTORC1 by adeno-associated virus 1 transduction with a gene encoding the constitutively active form of Akt or ras homolog enriched in the brain (Rheb) in substantia nigra DA neurons induces neurotrophic effects, including abilities to both protect and restore the nigrostriatal DA projections, in a neurotoxin mouse model of Parkinson's disease (Cheng et al., 2011; Kim et al., 2011, 2012). These results suggest that the activation of mTORC1 is required for the survival of DA neurons and functional maintenance of the DA system in the adult brain. In accordance with previous reports, we have recently reported that naringin-mediated neuroprotection in the MPP⁺ rat model of Parkinson's disease may be associated with the activation of mTORC1 (Leem et al., 2014). However, it is still unclear whether the activation of mTORC1 can reproduce neurotrophic factors through intracellular signaling pathways in adult neurons of the brain. We have recently found that increased expression of Rheb (S16H) by a viral vector induces a robust ability to induce GDNF in adult DA neurons *in vivo*, which is dependent on mTORC1 activity and contributes to the protection of the nigrostriatal DA

projection (Nam et al., 2014a). The results describe the relationships between GDNF reproduction and mTORC1 activation. To ascertain whether naringin mediates mTORC1 activity, we further examined the effects of naringin with or without mTORC1-specific inhibitor rapamycin on the activation of mTORC1 (**Figure 1**). Rats received daily intraperitoneal injection of rapamycin (5 mg/kg) or naringin (80 mg/kg), or co-injection of rapamycin and naringin for 4 days. Similar to the previous results (Leem et al., 2014), our results showed that treatment with naringin alone increased mTORC1 substrate phospho-4E-BP1 expression in the substantia nigra of rat brain compared to the intact controls, as shown by the results of western blot analysis (**Figure 1**). Rapamycin did not alter the baseline activity of mTORC1 in the substantia nigra. However, its treatment decreased the level of naringin-increased phospho-4E-BP1 (**Figure 1**), suggesting that naringin mediated mTORC1 activity for neurotrophic effects similar to the effects induced by the active Rheb in the substantia nigra (Nam et al., 2014a).

Another potential effect of naringin to protect the nigrostriatal DA projection is its anti-inflammatory activities. Brain and immune system are complicatedly connected and engage in crosstalk to maintain homeostasis. A number of evidences from human and animal studies have suggested that neuroinflammation is an important contributor to the neuronal loss in Parkinson's disease, and that long-term use of anti-inflammatory agents reduce the risk for Parkinson's disease (Gao et al., 2005; Chen et al., 2005). Parkinson's disease exhibits the activation of microglia, a resident immune cell of the brain, and activated microglia is involved in the loss of dopaminergic neurons in Parkinson's disease (Mount et al., 2007). Numerous microglial-derived neurotoxic factors, such as reactive oxygen species, inducible nitric oxide synthase and proinflammatory cytokines, can induce neuron death (Block and Hong, 2005; Colton et al., 2006; Yu et al., 2008; Kim et al., 2010; Nam et al., 2014b). Among them, TNF- α is one of proinflammatory cytokines which has received much attention due to its ability to promote the progressive degeneration of the DA projection (McCoy et al., 2006). A deficiency of TNF- α decreases dopamine content loss in the striatum after neurotoxin administration (Ferber et al., 2004). Null mice of TNF- α also showed protection against DA neurotoxicity (Sriram et al., 2002), suggesting an overall detrimental effect of TNF- α on the nigrostriatal DA system. In addition to the neurotrophic effects, we have found that naringin attenuates the level of TNF- α in the microglia increased by MPP⁺-induced neurotoxicity, which indicates the anti-inflammatory activity of naringin against inflammation in the substantia nigra (Leem et al., 2014).

As described in the preceding text, although GDNF has beneficial effects in models of Parkinson's disease, its direct infusion into the brain is necessary to achieve a therapeutic purpose. In addition, although gene therapy with viral vectors inducing neurotrophic effects such as mTORC1 activation similar to GDNF-mediated effects is still being investigated to treat Parkinson's disease patients, there are concerns about live virus administration and genetically

modifications of host neuronal cells. Thus, alternative therapeutic approaches such as natural compounds or chemical drugs can be useful to develop a protector of the nigrostriatal DA system in the adult brain, and many researchers have currently proposed intervention strategies using phytochemicals as an alternative approach against neurodegenerative diseases. In particular, phytochemicals are usually considered to be harmless to health with less toxic and fewer side effects than synthetic drugs.

Among various phytochemicals, naringin, which has found in grapefruits and citrus fruits in high concentrations (Jagetia and Reddy, 2002), has not only pharmacological anti-inflammatory and antioxidant activities but also neuroprotective effects against neurodegenerative disorders (Golechha et al., 2011; Gopinath et al., 2011; Chanet et al., 2012). Recently, we have also demonstrated the ability of naringin to prevent neurodegeneration (Leem et al., 2014). In a neurotoxin model of Parkinson's disease, treatment with naringin protects the nigrostriatal DA projection by increasing GDNF expression and decreasing TNF- α expression in DA neurons and microglia, respectively, which suggests that naringin can impart to the adult DA neurons the ability to reproduce GDNF as a therapeutic agent against Parkinson's disease with anti-inflammatory effects on brain inflammation. Thus, naringin may be a promising natural compound with neuroprotective activity and safety. However, there is lack of evidence for the neuroprotective roles of naringin in clinical trials, and there is still insufficient mechanisms of naringin-mediated effects on Parkinson's disease. Therefore, further studies are needed to evaluate detailed mechanisms of naringin-induced effects in the adult brain, except the GDNF-mediated pathway, and to investigate whether naringin can prevent and improve parkinsonism in humans. In addition, it may be worthwhile to test whether post-treatment with naringin can restore the function of DA neurons in the adult brain.

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