

● PERSPECTIVE

## Inhibition of microglial activation and induction of neurotrophic factors by flavonoids: a potential therapeutic strategy against Parkinson's disease

Parkinson's disease (PD) is characterized by the progressive degeneration of dopaminergic (DA) neurons and a decrease in striatal dopamine, which is associated with clinical movement disorders including a tremor at rest, rigidity of the limbs, bradykinesia (slowness and paucity of voluntary movement) and postural instability (a tendency to fall even in the absence of weakness or cerebellar balance disturbance) (Kim et al., 2012). Although the lack of fully understanding of the etiology of PD, accumulating evidence suggests that microglial activation (Kim et al., 2010) and insufficient support of neurotrophic factors (Kim et al., 2012; Nam et al., 2014) may be crucial for the initiation and progression of PD. Thus the control of microglial activation and the support of neurotrophic factors may be useful to prevent the degeneration of the nigrostriatal DA projections in the adult brain.

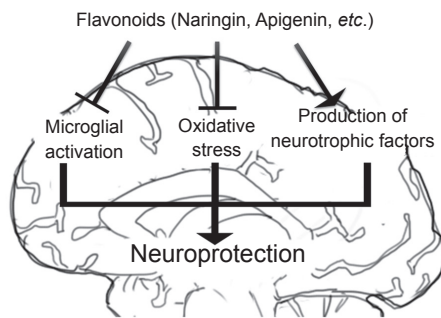
**Role of microglial activation in PD:** In the central nervous system (CNS), the inflammatory response (neuroinflammatory response) involves microglial activation that protects and supports CNS, even though severe activation of microglia can cause neurotoxicity in the adult brain. Microglia are resident immune cells in the brain, approximately 10% of the adult brain cell population, and those play a role for an important immune defense (Kim et al., 2010). Microglia are stimulated to derangement of homeostasis in CNS and transformed activated phenotype from their usual quiescent state. In the healthy brain, morphology of microglia in resting state is characterized by small cell body with ramified and tiny processes. Resting microglia indicate low level of inflammatory molecules expression associated with immune system. On the contrary to resting state, in neuropathological conditions such as neuropathogen and physical damage, microglia are changed to activating state, which is characterized by large cell body and shortened processes with a significant up-regulation of cytoplasmic and membrane molecules (Kim et al., 2010). For a defense immune system, acute microglial activation shows a positive function to minimize injury and promote tissue repair through removal of harmful pathogens. However, chronic microglial activation contributes to neurotoxicity by production of neurotoxic molecules such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), reactive nitrogen species (RNS) and reactive oxygen species (ROS) (Kim et al., 2010). PD patients and animal models of PD induced by neurotoxins such as 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) show similar chronic microglial activation, and its activation contributes to an exacerbation of neurodegeneration in the nigrostriatal DA system (Block and Hong, 2005; Kim et al., 2010). Moreover, several reports indicate that anti-inflammatory agents can protect DA neurons against neurotoxin molecules in animal models of PD (Block and Hong, 2005; Kim et al., 2010), and the use of anti-inflammatory agents can reduce the risk for PD (Block and Hong, 2005). These results suggest that the control of microglial activation may be useful to prevent the degeneration of the

nigrostriatal DA projections in the adult brain.

**Inhibition of microglial activation by flavonoids:** As described above, microglial activation is an important characteristic of neurodegenerative diseases such as PD, and the control of microglia-mediated inflammation can be considered as a potential therapeutic strategy against PD. There is a report showing the use of nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce risk of PD (Gurwitz et al., 1996). However, the chronic use of NSAIDs or other anti-inflammatory drugs could induce side effect. For instance, the chronic intake of ibuprofen can induce a serious increase in blood pressure (Gurwitz et al., 1996). To overcome this limitation, therefore, harmless nature compounds such as flavonoids can be considered as efficient materials for anti-inflammatory drugs against neurodegeneration.

Flavonoids are a class of plant secondary metabolites, and abundant polyphenols in edible plants and fruits. Those are divided into several groups according to their substitution group. Major groups of flavonoids, which are interested in the nutritional use, are flavanols, catechins, flavones and flavanones. Many kinds of flavonoids have powerful anti-oxidant effects, and the anti-oxidant properties induced by flavonoids depend on polyphenol substitution. Moreover, since flavonoids are small molecules and pass the blood brain barrier (BBB), they can reach into the brain by oral intake. However, the effects of flavonoids against PD are not well described yet, even though many studies have shown that various flavonoids have beneficial effects for anti-cancer, anti-cardiovascular diseases and anti-neurodegeneration. In recent years, research groups have reported the bio-availability of flavonoids against neurodegeneration involved in PD, and many results showed that lots of flavonoids have an important ability to attenuate microglial activation and inflammatory responses in the models of PD *in vivo* and *in vitro* (Lee et al., 2014; Patil et al., 2014). We also reported that flavonoids such as naringin, nobiletin and silibinin can induce neuroprotective effects through a suppression of microglial activation in animal models of PD (Jeong et al., 2014; Jung et al., 2014; Leem et al., 2014). Intraperitoneal injection of naringin, one of the abundant flavonoids in grape fruit and citrus fruits, could attenuate the levels of TNF- $\alpha$  induced by activated microglia in the 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>)-treated animal model of PD (Leem et al., 2014). Nobiletin (Jeong et al., 2014) and silibinin (Jung et al., 2014), extracted from citrus peels and milk thistle, respectively, showed the similar inhibitory effects on activated microglia-induced neurotoxic molecules such as TNF- $\alpha$ , IL-1 $\beta$  and inducible nitric oxide synthase (iNOS) in the animal model of PD. These results suggest that many kinds of flavonoids can play a role as anti-inflammatory agents in the adult brain, and consequentially contribute to neuroprotection against PD, even though the inhibitory mechanism of flavonoids such as naringin, nobiletin and silibinin on microglial activation must be clarified in the further study.

**Neuroprotective effects of GDNF and BDNF in PD:** Chauhan et al. (2001) have reported that DA neurons in the substantia nigra (SN) of PD patient's brains express decreased levels of glial cell line-derived neurotrophic factor (GDNF) or brain-derived neurotrophic factor (BDNF), suggesting that GDNF and BDNF are an indispensable neurotrophic factor for the survival and protection of DA neurons. Moreover, there are many reports showing neuroprotective effects of GDNF and BDNF in animal models of PD (Nam et al., 2014).



**Figure 1** Schematic representation of flavonoids-induced neuroprotective effects.

Many kinds of flavonoids can attenuate microglial activation and oxidative stress, and induce neurotrophic factors to protect dopaminergic neurons in the adult brain.

Direct injection of GDNF into the SN or striatum could induce an increase in the density of DA fibers and improve abnormal motor system in the MPTP-treated animal model of PD, and conditional ablation of GDNF in adult mice results in a delayed and progressive loss of DA neurons (Nam et al., 2014). The infusion of an antisense oligonucleotide specific to BDNF results in anatomical, neurochemical and behavioural deficits characteristic of neurotoxic models of PD (Nam et al., 2014), indicating that reduced BDNF expression contributes to the degeneration of DA neurons. Although the evidence suggests that GDNF and BDNF are potent neurotrophic factors for the survival and protection of DA neurons in PD, there is a critical problem of using those factors for PD treatment. GDNF and BDNF must be directly treated in the brain to apply to PD patients because those do not cross the blood-brain barrier which is the brain's protective membrane. Moreover, clinical trials which intracerebroventricular injection and intraputamin infusion of GDNF not only fail to treat parkinsonism, but also caused several side effects such as nausea, anorexia and vomiting (Nam et al., 2014). Thus, replacement strategies supporting neurotrophic factors are considered as potential therapeutics for PD.

Induction of neurotrophic factors in DA system by treatment with flavonoids: Many kinds of flavonoids can induce brain to produce neurotrophic factors such as GDNF and BDNF against neurodegeneration (Jeong et al., 2014; Leem et al., 2014; Patil et al., 2014). However, it was unclear whether treatment with flavonoids can induce neurotrophic factors in DA neurons *in vivo*. Patil et al. (2014) reported that flavonoids such as apigenin and luteolin could induce BDNF in the nigrostriatal DA system in mice. Similar to these trophic effects induced by apigenin and luteolin, we found that flavonoids such as naringin and nobiletin could induce GDNF in the substantia nigra pars compacta (SNpc) of rat brains, and its expression increased by treatment with naringin and nobiletin was preserved in the MPP<sup>+</sup>-treated animal model of PD (Jeong et al., 2014; Leem et al., 2014). Moreover, naringin could activate mammalian target of rapamycin complex 1 (mTORC1), which is necessary for the survival of DA neurons in SNpc (Leem et al., 2014; Kim et al., 2012). Taken together, these results suggest that many kinds of flavonoids may have an important ability to induce neurotrophic factors, which can contribute to neuroprotection against PD.

**Flavonoids, potential therapeutic medicines against PD:** Flavonoids such as naringin, nobiletin, silibinin, apigenin and luteolin induce neuroprotective effects through inhibition of

inflammatory reactions and oxidative stress, and induction of neurotrophic factors in animal models of PD (Figure 1). These results suggest that many flavonoids may be beneficial natural products offering promise for the prevention of neurodegeneration involved in PD. However, it is still unclear whether post-treatment with effective flavonoids can restore the function of DA neurons in adult brains. Therefore, to make the possibility to treat PD patients clear, further study is needed to determine the effects of post-treatment with flavonoids such as the induction of dopamine and the regeneration of axons after damage in DA system of adult brain as well as the study on the mechanisms of flavonoids-induced effects in the adult brain.

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