

The neuroprotective effects of apocynin

Agnes Simonyi^{1,2}, Peter Serfozo¹, Tareq M. Lehmidi^{2,3}, Jiankun Cui^{2,3}, Zezong Gu^{2,3}, Dennis B. Lubahn¹, Albert Y. Sun^{2,3}, Grace Y. Sun^{1,2,3}

¹Department of Biochemistry, University of Missouri, Columbia, MO, ²Center for Translational Neurosciences, University of Missouri, Columbia, MO, ³Department of Pathology and Anatomical Sciences, University of Missouri, Columbia, MO

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1. ABSTRACT

The recognition of health benefits of phytomedicines and herbal supplements lead to an increased interest to understand the cellular and molecular basis of their biological activities. Apocynin (4-hydroxy-3-methoxy-acetophenone) is a constituent of the Himalayan medicinal herb *Picrorhiza kurroa* which is regarded as an inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, a superoxide-producing enzyme. NADPH oxidase appears to be especially important in the modulation of redox-sensitive signaling pathways and also has been implicated in neuronal dysfunction and degeneration, and neuroinflammation in diseases ranging from stroke, Alzheimer's and Parkinson's diseases to psychiatric disorders. In this review, we aim to give an overview of current literature on the neuroprotective effects of apocynin in the prevention and treatment of neurodegenerative disorders. Particular attention is given to *in vivo* studies.

2. INTRODUCTION

Apocynin (4-hydroxy-3-methoxy-acetophenone) was first isolated from *Apocynum* species. Two North American species of *Apocynum*, *A. androsaemifolium* and *A. cannabinum*, were widely used by Native American tribes as medicine (1). In addition, *Apocynum venetum* is used as a tea in north China and Japan and reported to have hepatoprotective effects (2). Apocynin may also be obtained from other plants, e.g. from the rhizome of *Iris* species.

Apocynin was discovered during activity-guided isolation of immunomodulatory constituents from *Picrorhiza kurroa*, an endangered medicinal plant native to the mountains of India, Nepal, Tibet and Pakistan. *Picrorhiza kurroa* has been used to treat liver diseases, upper respiratory tract disorders, chronic diarrhea, scorpion sting and fever in the Ayurvedic system of medicine (3). In traditional Chinese medicine, *Picrorhiza* has been used to treat hyperemia and dysentery, hemorrhoids, epilepsy and

carbuncles (3). Currently, the extracts of *Picrorhiza kurroa* are used as a complementary and alternative medicine.

It is important to note that no adverse side effects of *Picrorhiza* extract/apocynin have been reported (3). Apocynin has a very good safety profile in animal studies as well (4), and several studies used long-term treatment without any signs of ill-health effects (see the studies with transgenic mice of Alzheimer's disease, for an example). Our recent study on the bioavailability of apocynin showed that apocynin is rapidly metabolized into glucuronic conjugate (5). At 30 min and 1 h after injection (5 mg/kg body wt, i.p.), approximately 50% of apocynin was converted to its glucosyl derivative and was distributed in plasma, liver and brain. Apocynin appeared in plasma as early as 30 min, peaked at 1 h and declined to low levels after 2 h (5). Following intragastric administration, apocynin is shown to undergo rapid absorption and excretion; with urinary excretion containing the unchanged form, the glucuronide, demethylated, ring-hydroxylated form as well as other derivatives, and fecal recoveries of the metabolites were small (6).

Apocynin has been found to exhibit powerful anti-oxidant and anti-inflammatory effects in a variety of *in vitro* and animal models. It is an inhibitor of NADPH oxidase with an IC_{50} of 10 μ M (7). The prototypic NADPH oxidase comprises a membrane-associated cytochrome b_{558} composed of one p22 phox and one gp91 phox subunit and several regulatory cytosolic subunits (p47 phox, p40 phox, p67 phox and the GTPase Rac1 or Rac2) that translocate to the membrane and associate with the cytochrome b_{558} and thus activating the oxidase and generating a large amount of $O_2^{\cdot -}$ in the process. Although the precise molecular mechanism is still not clear, apocynin was thought to block the activity of NADPH oxidase by interfering with the assembly of the cytosolic NADPH oxidase components with the membrane components (8). Apocynin can be easily oxidized by peroxidases such as myeloperoxidase, resulting the production of dimer and trimer derivatives (9). Diapocynin is a more efficient inhibitor of NADPH oxidase than apocynin itself (10-12). It is assumed that peroxidase catalysis is necessary for the NADPH oxidase-inhibitory effect of apocynin, and that apocynin may act as a scavenger in cells with low levels of peroxidases (4, 13). Apocynin can also serve as a pro-oxidant, although the conditions have not been clearly defined (14).

3. NADPH OXIDASE AS A SOURCE OF OXIDATIVE STRESS IN NEURODEGENERATIVE DISEASES

Animal and human studies have indicated a fundamental role of reactive oxygen species (ROS) in the pathogenesis of neurodegenerative disorders, and NADPH oxidase has been shown to be one of the major sources of ROS production in the brain (15-17). Several isoforms of NADPH oxidase are expressed in the central nervous system (15); however, this review will not discuss the many different isoforms but focus on the prototypic NADPH oxidase (recently termed NOX2) because of this review's focus on apocynin. The role of NOX2 in neurodegenerative processes has been extensively studied on microglia, but

less is known regarding its function in astrocytes or neurons.

Relatively high levels of NOX2 are found in glial cells, as compared with neurons (18), and ROS produced from these cells have been shown to cause neuronal damage (19). ROS produced by NADPH oxidase can act as second messengers for mediating specific redox-sensitive signaling pathways (MAPKs, PI3K/Akt, NF-kappaB) involved in the inflammatory response. Glial activation is associated with the release of superoxide, NO, cytokines, phospholipases and proteases. The expression of some of these proinflammatory proteins, including the subunits of NADPH oxidase, cyclooxygenase-2 (COX-2), secretory phospholipase A2 (sPLA2-IIA), and inducible nitric oxide synthase (iNOS), are regulated by NADPH oxidase. Recent studies including ours have demonstrated that apocynin inhibits the induction of iNOS, sPLA2-IIA, COX-2 and cytokines (20-22), and prevents inflammation-mediated toxicity to neurons (23-25). Using neuron-glial cell co-culture, peroxynitrite was shown to be produced by NO release from iNOS and ROS from NADPH oxidase in glial cells, and peroxynitrite is a potent cytotoxic factor for killing neurons (26).

4. STROKE AND BRAIN INJURIES

Stroke is an interruption of blood flow to the brain caused by a block in cerebral artery (ischemic stroke) or a burst in cerebral blood vessels (hemorrhagic stroke). The pathophysiological processes in stroke are extremely diverse and dependent on the severity, duration and localization of the damage in the brain. Mechanisms of ischemia/reperfusion-induced brain tissue damage are complex, including glutamate neurotoxicity, calcium overload, the release of cytokines, and infiltration of inflammatory cells into the tissue; among these, the production of ROS during the reperfusion state is a major factor contributing to tissue injury. ROS produced during reperfusion can initiate a series of cellular events that eventually lead to inflammation, necrosis and/or apoptosis. Furthermore, ROS can directly damage lipids, proteins and nucleic acids, and modulate intracellular signaling pathways necessary for the regulation of inflammatory gene expression. Despite the involvement of these changes in ischemic injury and brain damage, some can also regulate neuroprotective changes and mediate tissue repair. Accumulating evidence has shown that activation and/or overexpression of NADPH oxidase occurs during ischemia/reperfusion and contributes directly to oxidative injury through indirect signaling pathways. Animals deficient in gp91 phox have reduced infarct damage (27-29). Both *in vitro* and *in vivo* studies have shown that NADPH oxidase-derived ROS are the key regulators of inflammatory response and mediate proinflammatory gene expression in glial cell (30, 31). The neuroprotective effect of NADPH oxidase inhibition involves the suppression of inflammatory pathways in ischemia (32-34).

The neuroprotective effects of apocynin in ischemic injury have been frequently studied using animal models, especially rodents, and with either focal or global

cerebral ischemia (Table 1.). The most important findings are: (1) systemically administered apocynin is neuroprotective in cerebral ischemia – improvement in functional outcome and decreased brain damage; (2) effective applications of apocynin need to be administered prior to ischemia/reperfusion and at relatively low doses; (3) apocynin does not influence the mortality rate after cerebral ischemia; (4) apocynin does not influence stroke damage in gp91 phox knockout animals (35). Furthermore, one study showed that apocynin exacerbates stroke damage in aged animals (36). Our recent study used a dietary preventative protocol in which apocynin was added into the drinking water so that animals received 50 mg/kg dose each day for 5 days before surgery. C57BL/6J male mice (23–27 g) were subjected to 120 min of focal ischemia induced by middle cerebral artery occlusion using a 6-0 monofilament suture and followed by 24 h reperfusion as described by Gu *et al.*, 2005 (37). Brains were dissected and cut into 1-mm coronal sections for 2,3,5-triphenyltetrazolium chloride (TTC) staining to quantify the infarct volumes. To minimize the effect of brain edema, the infarct volume was determined by subtracting the volume of the contralateral noninfarcted hemisphere (left) from the ipsilateral hemisphere (right). As a functional outcome, the rotarod test was chosen. Each day for 2 days prior to ischemia, mice were trained on the rotarod in the acceleration paradigm (3–30 rpm/5 minutes) in two trials with a 10-min inter-trial interval. Measurement of latency, i.e. the time spent on the rotating rotarod without falling off or gripping and spinning rather than walking, was used to assess performance. In this study, apocynin administration resulted in a significant decrease in infarct volume and improved functional outcome (Figure 1).

Studies show different time courses of NADPH oxidase activity and its subunits expression after different types of ischemia/reperfusion. In the transient global cerebral ischemia models, upregulation of the cytosolic subunits (p47 phox and p67 phox) was shown as early as 3 h after reperfusion and continued until 6 h, and then followed by a late phase at 72 h (38). The membrane bound gp91 phox subunit expression was increased between 24 h and 72 h and remain elevated until 7 days (38, 39). At 72 h after reperfusion, NADPH oxidase expression was detected in microglia (38). In focal cerebral ischemia, an increase in NADPH oxidase activity in the penumbral regions was demonstrated at 2 h after reperfusion (40, 41); whereas, other studies showed an increase after 24 h (42, 43). A significant increase in gp91 phox expression was found between 1 h and 24 h after reperfusion in the peri-infarct area (27, 40, 44). In mice, a 20 min middle cerebral artery occlusion induced an early increase in gp91 phox mRNA expression, an event preceding iNOS expression (45). Enhanced expression of other subunits, p22 phox, p47 phox (but see Kusaka *et al.*, 2004) (46) and p67 phox has also been reported (40, 45, 47). Immunohistochemical studies demonstrated that the increase in NADPH oxidase subunits overexpression after transient focal cerebral ischemia is derived mainly from activated microglia (48).

The neuroprotective effects of apocynin in hemorrhagic stroke are less conclusive. Apocynin (5

mg/kg, i.p., 3 times daily for 2 days after surgery) attenuated vasospasm and reduced neurological deficits after experimental subarachnoid hemorrhage in rats (49). However, apocynin treatment (3, 10 and 30 mg/kg, i.p., 2 h after surgery) did not improve the outcome after intracerebral hemorrhage in rat (50).

Spinal cord injury is the result of an initial physical trauma followed by a secondary degenerative process. These secondary inflammatory processes may play a key role in the expansion of the lesion size. Myeloperoxidase and gp91 phox are expressed by neutrophils, activated microglia, and macrophages in the injured human spinal cords, with maximum expression observed at 1–3 days after injury (51). Apocynin (5 mg/kg, i.p.) significantly improved motor recovery and decreased tissue injury and inflammation when applied 1 h and 6 h after spinal cord injury to mice (52). The same dose of apocynin was also effective in a mouse cold injury model (53). NADPH oxidase-derived ROS overproduction also contributes to neurodegeneration in traumatic brain injury (54), but the effects of apocynin have not been examined.

5. ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is regarded as the most common form of dementia in the elderly leading to a progressive impairment of memory, cognition, language and behavior. Beta-Amyloid (A β) plaques and hyperphosphorylated tau-containing neurofibrillary tangles are the pathological hallmarks of AD, which is associated with an increase in oxidative and inflammatory processes in specific brain regions. The upregulation of cortical NADPH-oxidase in AD implies that increases in NADPH oxidase-associated redox pathways might participate in early pathogenesis and contribute to AD progression (55–57).

A β has been reported to increase the generation of ROS by NADPH-oxidase in neurons, microglia, monocytes, neutrophils and astrocytes (58–61), and apocynin is neuroprotective in cell culture models of AD (62, 63). There is convincing evidence suggesting a role for glial cell NADPH oxidase in A β -induced neurotoxicity (19, 64–67). Furthermore, the cytotoxic effects of familial AD-causative mutants could be inhibited by apocynin (68, 69). However, chronic apocynin treatment failed to improve cognitive deficits in transgenic mouse models of AD, although some positive changes in neuropathology have been shown. The first study used Tg19959 mice (hAPP₆₉₅ with the London and Swedish mutations) and 4 month of apocynin administration (from 1 month of age until 5 months of age) in the drinking water at the dose of 300 mg/kg/day (70). There were no changes in amyloid and tau pathology and microgliosis. However, apocynin reduced protein carbonyl levels in the cortex. Although NADPH oxidase activity did not show changes in the Tg19959 mice, Rac1 expression was significantly elevated and apocynin treatment normalized Rac1 levels in the brain (70). The second study used 10 mg/kg/day apocynin for 4 months given by gavage to hAPP₇₅₁ mice (neuron-specific expression of hAPP₇₅₁ with the

Table 1. Neuroprotective effects of apocynin in rodent cerebral ischemia models

Effective treatment	Model, animal	Effects (infarct, behav)	Outcomes measured	References
Focal cerebral ischemia				
5 mg/kg, i.p. 30 min before I	120 min, rat	+	edema, BBB, SOD, GPx, CAT, MDA	(36)
5 mg/kg, i.p. 30 min before I	120 min, rat	+	superoxide, gp91 phox expr	(44)
7.5 mg/kg/day in diet for 4 weeks	120 min, rat	-		(44)
5 mg/kg, i.p. 5 min before R	120 min, rat	+	IL-1 β , ICAM-1, IkappaB-alpha, Bax, Bcl-2, nitrotyrosine	(109)
5 mg/kg, i.p. 30 min before I and 5 min after R	90 min, rat	+	PSD proteins, p67 phox expr	(47)
50 mg/kg, i.p. 30 min before I	90 min, rat	+	NADPH oxidase activity, superoxide	(41)
30 min/kg, i.p. 60 min before I	90 min, rat	+	gp91 phox, MMP9 expr in microvessels	(110)
40 mg/kg, i.v. 60 min before I	120 min, mouse	+	BBB	(28)
2.5 mg/kg, i.v. 30 min before R	120 min, mouse	+	BBB, superoxide	(111)
4 mg/kg, i.p. 5 min before R	75 min, mouse	+	MDA, 8-OHdG, ICAM-1, MPO, COX2	(27)
4 mg/kg, i.p. 5 min before R	60 min, mouse	ND	IBA-1, nitrotyrosine	(32)
2.5 mg/kg, i.p. 30 min before I	30 min, mouse	+	superoxide	(35)
2.5 mg/kg, i.p. 60 min after R	30 min, mouse	-		(35)
Global cerebral ischemia				
5 mg/kg, i.p. 30 min before I	5 min, gerbil	+	HNE, Fluro-Jade B, MAP-2, 8-OHdG	(112)
15 mg/kg, i.p. before R	30 min, mouse	+	superoxide	(113)
2.5 mg/kg, i.v. 15 min before I	22 min, mouse	+	superoxide, gp91 phox, p47 phox, p67 phox expr	(38)
40 mg/kg, i.p. 10 min before I	20 min, mouse	+	superoxide, gp91 phox, Rac1, p47 phox expr	(39)

Infarct, infarct size or cell death; behav, behavioral outcome; I, ischemia; R, reperfusion; BBB, blood-brain barrier; PSD, postsynaptic density; expr, expression; + neuroprotective effect; - no effect; ND, not determined

London and Swedish mutations) starting at 4 months of age (71). There was a significant reduction in plaque load in the cortex and the hippocampus, and apocynin treatment also decreased the number of microglia in the cortex. However, at 8 months of age, there were no substantial changes in inflammatory and oxidative stress markers in the brain of hAPP (751)^{SL} mice and apocynin administration did not alter these parameters. These results suggest that some beneficial effects of apocynin are independent of its anti-inflammatory and anti-oxidative properties (71).

6. PARKINSON'S DISEASE

Parkinson's disease (PD), similarly to AD, is an age-related, progressive neurodegenerative disorder that affects movement and is characterized by the loss of dopaminergic neurons in the nigrostriatal system. Although the clinical and pathological features of PD are complex, neuroinflammation and oxidative stress are strongly implicated in the pathogenesis and reviewed by (72, 73). An increase of gp91 phox expression was found in ventral midbrain samples of PD subjects (74). Accordingly, recent studies using genetic deletion of gp91 phox have shown that microglial activation and NADPH-oxidase-derived free radicals play major roles in the toxicity of a variety of compounds leading to dopaminergic neuronal death (75, 76). Apocynin has been used effectively to inhibit neurotoxicity for 6-OHDA (77), MPTP/MPP⁺ (75, 78),

neuromelanin (79) and environmental neurotoxins such as paraquat (80, 81), rotenone (82) and formyl-methionyl-leucyl-phenylalanine (83) *in vitro* with dopaminergic neurons, neuron-glia co-cultures or slice culture preparations. Most importantly, apocynin is also beneficial when used *in vivo* in different animal models of PD; preadministration of apocynin protects against paraquat-induced dopaminergic cell death in mice (80) and 6-OHDA-induced neurodegeneration in rats (84).

7. OTHER NEUROLOGICAL AND PSYCHIATRIC DISORDERS

Several reports suggest that NADPH oxidase might also be implicated in other diseases such as Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), epilepsy, HIV-associated dementia, schizophrenia, alcohol-induced neurodegeneration, and sleep disorders.

ALS is a progressive degenerative disease affecting motor neurons. Expression of NADPH oxidase is increased in the spinal cord of ALS patients, especially in microglia (85). Inherited dominant mutations in superoxide dismutase-1 (SOD1) are associated with the familiar forms of ALS. Crossing SOD1 transgenic mice with gp91 phox knockout mice resulted in an improvement of symptoms and pathology and extended survival (85, 86). Long-term apocynin treatment (30, 100 or 300 mg/kg/day in the drinking water) significantly delayed disease progression in

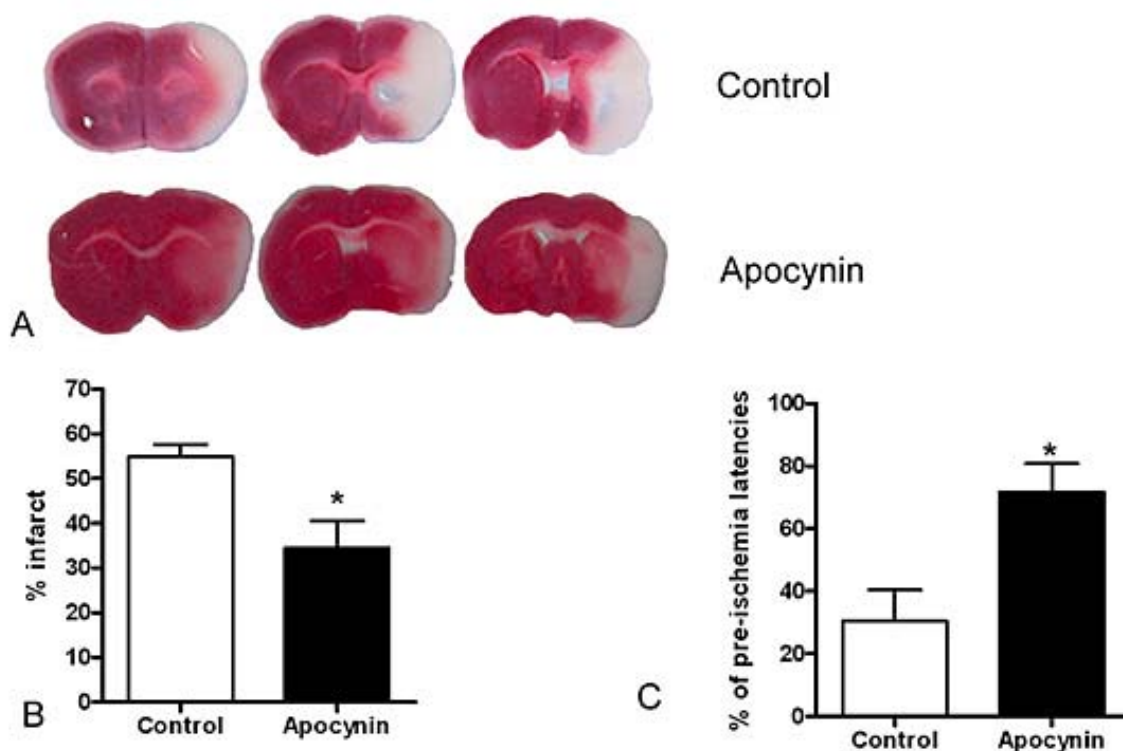


Figure 1. Decreased brain infarct volume and improved behavioral outcome after ischemia/reperfusion in mice with apocynin administration, A) Representative photographs of TTC staining at 24 h of reperfusion after a 2 h middle cerebral artery occlusion, B) Quantification of infarct volume (Data are mean \pm SEM; n=5-6, *p<0.05 vs. control), C) Rotarod performance (Data are mean \pm SEM; n=5-6, *p<0.05 vs. control)

the transgenic mice (87). In organotypic spinal cord slice culture, inflammation-induced toxicity to motor neuron can be prevented by apocynin (24). Apocynin also attenuates neurotoxicity by glial cells expressing SOD1 mutants (87, 88).

HD is a rare inherited neurological disorder characterized by abnormal body movements, lack of coordination, and a decline in cognition functions. Intrastriatal injection of quinolinic acid is used as an experimental model of HD; quinolinic acid causes excitotoxicity, and induces some neurodegenerative and behavioral changes similar to those observed in HD (89). Apocynin injection (5 mg/kg, i.p.) to rats either before and after, or just after quinolinic acid infusion decreased circling behavior. However, both injections are necessary for the protection of the striatal tissue and prevention of an increase in oxidative stress (90).

Temporal lobe epilepsy is clinically described by the progressive development of spontaneous recurrent seizures from temporal lobe foci, and pathophysiological changes include extensive neuronal loss, gliosis and axon reorganization. In the pilocarpine model of epilepsy, neurodegeneration occurs in the hippocampus, first in the dentate gyrus, later in the CA1 and CA3 regions (91). Apocynin (10 mg/kg/day in the drinking water) administration for 7 days before pilocarpine treatment leads to significant neuroprotection in all three brain areas (92).

HIV-associated dementia, the most severe form of HIV-associated neurocognitive disorders, features motor and behavioral dysfunctions leading to seizures, coma, and death. HIV-encephalitis, the pathological correlate of HIV-dementia, is a neurodegenerative disease with increased gliosis, neuroinflammation and oxidative stress (93). Using an *in vitro* model, HIV-1 Tat treatment in astrocytes, a recent study demonstrated that apocynin pretreatment inhibited oxidative signaling and inflammatory processes and decreased neurotoxicity (94). Apocynin can also protect neurons against the viral toxin, gp120-induced cell toxicity (95).

Schizophrenia is marked by disturbances in cognitive functions, emotional reactions, behavior, with delusions and hallucinations. The pathophysiology of schizophrenia is complex and involves many different cortical and subcortical systems. Recently, it was suggested that NADPH oxidase might play a role in the pathogenesis of schizophrenia and ketamine-induced psychosis (96). Prolonged administration of ketamine leads to dysfunction of the parvalbumin-interneurons in the cortex, and apocynin (5 mg/kg/day in the drinking water) prevented the ketamine effects (97).

Sleep apnea is a sleep disorder in which there are pauses in breathing or reductions of breath amplitude. Long-term intermittent hypoxia, a model of sleep apnea, is

characterized by the activation and increased expression of NADPH oxidase, oxidative and inflammatory responses in specific brain regions, and spatial learning deficit (98). Apocynin (3 mg/kg/day) given by gavage to rats or s.c. to mice prevented hypersomnolence, the increase in proinflammatory gene expression and oxidative damage, as well as decreases in spatial learning and reduced catecholaminergic neuronal injury (99-101).

Apocynin also showed efficacy against alcohol-induced neurodegeneration (44, 102), in pain management (103), and in models of hepatic encephalopathy (104, 105).

8. PERSPECTIVE

Recognition of the important role of NADPH oxidase in physiological and pathological processes has highlighted the need to identify compounds that directly modulate the activities of NADPH oxidase, either through binding to specific protein subunits or through scavenging the ROS produced. Plant flavonoids are potent inhibitors of NADPH oxidase. A study of 45 compounds indicated that flavanols inhibit NADPH oxidase through an apocynin-like mechanism (12). Other studies have demonstrated the ability of specific botanical compounds to inhibit NADPH oxidase by directly binding to p47 phox (kaempferol) (106), or disrupting the binding of the proline rich region of p22 phox to the tandem SH3 domain of the cytosolic subunits (celastrol) (107). Some polyphenols also have been shown to modulate NADPH oxidase subunit expression (108). Clearly, further studies are necessary to test apocynin (and its metabolites), especially its long-term efficacy, and other NADPH oxidase inhibitors in a variety of animal models of neurodegenerative diseases, and to accumulate additional information about mechanisms of action. Investigations of apocynin's effects in neurodegeneration have been performed in a very wide range of concentrations, affecting the possibilities of alternative mechanisms and/or "side effects" besides NADPH oxidase inhibition. In future studies it is crucial that mechanisms are verified. Careful investigations will also aid to the thorough characterization of the roles of NADPH oxidase in neurodegeneration.

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Send correspondence to: Agnes Simonyi, Department of Biochemistry, 117 Schweitzer Hall, University of Missouri-Columbia, Columbia, MO 65211, Tel: 573-884-6178, Fax: 573-882-5635, E-mail: simonyia@missouri.edu

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