

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Hypertension 2010, 56:e34: originally published online August 9, 2010
doi: 10.1161/HYPERTENSIONAHA.110.158170

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX
72514

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ISSN: 1524-4563

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To the Editor:

In a recent issue of *Hypertension*, Rezzani et al reported that 6 weeks of treatment with either melatonin or pycnogenol, a pine bark extract rich in flavonoids, protected structure and function of the microvasculature in spontaneously hypertensive rats and resulted in a reduction in systolic blood pressure.¹ These effects were ascribed to the antioxidant properties of both compounds that reduce oxidative stress and increase the availability of nitric oxide by several mechanisms as depicted in the figure in the accompanying editorial.² We would like to propose reduction of the activity of the oxidative enzyme myeloperoxidase (MPO) as an additional mechanism.

MPO, an enzyme linked to both inflammation and oxidative stress, catalyzes the production of hypochlorous acid and a range of other highly reactive species, which, by killing pathogens, play a protective role in the innate immune response. In the vasculature, however, these MPO-derived reactive substances may lead to structural damage and reduce the bioavailability of the endogenous vasodilator nitric oxide. Accordingly, MPO is associated with the initiation and propagation of cardiovascular disease.³ We recently observed a positive association between levels of MPO and both systolic and diastolic blood pressure in a population-based cohort of elderly subjects.⁴ Because hydrogen peroxide is an obligate cosubstrate of MPO, the activity of MPO in the vasculature is enhanced by increased local production of reactive oxygen species. In other words, MPO has the ability to amplify oxidative stress, by using hydrogen peroxide to form reactive oxidant species with a higher oxidative potential. In accordance with this notion, the relationship between MPO and blood pressure was strongest in individuals with features associated with increased oxidative stress, such as obesity, low levels of high-density lipoprotein cholesterol, the metabolic syndrome, and type 2 diabetes.⁴

Interestingly, Galijasevic et al identified melatonin as a potent inhibitor of MPO.⁵ They showed that, at physiological and supplemental concentrations, melatonin interferes with the cata-

lytic activity of MPO by multiple pathways, including switching the activity of MPO from peroxidation to catalase-like activity and conversion of MPO to an inactive form.

Next to inhibition of MPO, melatonin may also reduce the activity of MPO in the vasculature by 2 other mechanisms that may also apply to pycnogenol. First, both compounds are potent scavengers of reactive oxygen species and may thereby limit the production of hydrogen peroxide, the cosubstrate of MPO. Second, the antiinflammatory properties of melatonin and pycnogenol may reduce infiltration of the vascular wall by MPO-secreting leukocytes.

In summary, we propose that, in addition to the mechanisms suggested by Rezzani et al, a reduction of vascular MPO activity likely contributes to the vasoprotective and blood pressure-lowering effects of melatonin and pycnogenol.

Disclosures

None.

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