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COMMENTARY

Therapeutic potential of *Schisandra chinensis* extracts for treatment of hypertension. Introduction to: 'Antihypertensive effect of gomisin A from *Schisandra chinensis* on angiotensin II-induced hypertension via preservation of nitric oxide bioavailability' by Park *et al.*

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Schisandra chinensis (SC) (五味子, wú wèi zi, 'five flavor berry') (family *Magnoliaceae*) is a medicinal plant whose fruits are commonly used in Asian traditional medicine for their sedative/hypnotic, hepatoprotective[1] and antioxidant[2] properties. In 1979, lignan phytoestrogens, known as 'Gomisins', were first isolated as the active agents of SC.[3] Since then numerous Gomisins (-A, -B, -C, -D, -F, -J, -G, -K, -N) have been described, and, as of 2012, a PubMed search for 'Gomisin' shows 102 citations, with 50% of these articles being published since 2005. Among the Gomisins, Gomisin A (GA) has been the one most widely studied (88 of 102 citations), owing to recent interest in its antihypertensive properties.[4] In the current issue of *Hypertension Research*, Park *et al.*[5] consider several potential mechanisms underlying the benefits of GA for angiotensin II (Ang II)-induced hypertension.

In Park's study, a C57B6 mice model of hypertension induced by Ang II infusion was employed. The authors found that a low dose of Ang II ($1\,\mu g\,kg^{-1}\,min^{-1}$), which was not effective at raising blood pressure, was able to reduce the tonic production of nitric oxide (NO). This NO suppression effect was also seen in mice receiving a higher dose of Ang II ($2\,\mu g\,kg^{-1}\,min^{-1}$) that did increase blood pressure. Therefore, an early and important effect of Ang II on endothelial cells may be to reduce NO formation. This depression in NO formation may synergize with the Ang II receptor-1 (AT1)-mediated activation of vascular smooth muscle contraction to elicit a strong, coordinated and sustained contraction.

Importantly, the current Park *et al.* study shows that GA is able to block Ang II-induced formation of superoxide and simultaneously maintain the tonic release of NO, apparently by maintaining the phosphorylation of endothelial NO synthase (eNOS). While a prior 2009 study by Park *et al.*[4] did not find an increase in eNOS phosphorylation in cultured human coronary artery endothelial cells, the current study finds a reduced eNOS phosphorylation when Ang II stimulation is used. This finding might have been missed because stimuli that depress eNOS phosphorylation (for example, Ang II) were not previously considered. Thus, an important effect of GA appears to be the maintenance of eNOS phosphorylation in the presence of stimuli that normally interfere with this process. Interestingly, GA significantly reduces blood pressure, apparently through NO/superoxide-mediated pathways. This finding indicates that in order for Ang II to strongly support vasoconstriction, the suppression of NO release may be a prerequisite step, which is permissive for maximal calcium/actomyosin-dependent contraction. Without relief from this first signal, vasoconstriction appears to be significantly weaker.

GA appears to promote vasodilation through both endothelial-dependent and independent mechanisms.[6] Maintaining endothelial NO production appears to be the endothelial-dependent mechanism, whereas preventing the formation of superoxide and the dephosphorylation of myosin light chain (MLC) in smooth muscle cells could be the endothelial-independent mechanism regulated by GA. In addition, inhibition of the RhoA/Rho-kinase-mediated activation of MLC phosphatase could be another GA-mediated endothelial-independent mechanism of vasodilation.[7]

Here, a scenario exists where eNOS phosphorylation (but not eNOS expression) appears to be suppressed by Ang II, and GA is able to maintain NO production in a manner that does require eNOS phosphorylation. This suggests that GA is able to acutely induce the activation of eNOS and may also maintain eNOS activity by maintaining eNOS phosphorylation. This might involve the inhibition of eNOS phosphatases (for example, protein phosphatase (PP)2A, which dephosphorylates eNOS serine 1179). Interestingly, in cultured neuronal cells, Ang II has been shown to stimulate PP2A.[8,9] Although the receptor subtypes mediating these phenomena are not the

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subject of the study by Park *et al.*, the endothelial AT2 receptor may balance signaling through the AT1 receptor to maintain endothelial NO metabolism,[10,11] and eNOS Ser1179 phosphorylation mediated by AT2 receptors has been reported in arterial endothelial cells.[12] In particular, AT2 receptors appear to be coupled to activation of the protein phosphatase PP2A. Ang II also activates the phosphatase calcineurin through AT1 receptors, an effect that is blocked by Losartan.[13] It would be interesting to investigate whether GA can interfere with Ang II-mediated AT1 activation or AT1R expression in these vascular tissues.

In conclusion, GA appears to promote vasodilation through several mechanisms, including maintenance of eNOS phosphorylation, scavenging of superoxide, possible inhibition of NADPH oxidase and interference with signals controlling actomyosin activation. Thus, SC extracts such as GA may have potential for treating hypertension in the future.

1 Takeda S, Maemura S, Sudo K, Kase Y, Arai I, Ohkura Y, Funo S, Fujii Y, Aburada M, Hosoya E. Effects of gomisin A, a lignan component of Schizandra fruits, on experimental liver injuries and liver microsomal drug-metabolizing enzymes. *Nihon Yakurigaku Zasshi* 1986; **87**: 169–187.
2 Wang JP, Raung SL, Hsu MF, Chen CC. Inhibition by gomisin C (a lignan from Schizandra chinensis) of the respiratory burst of rat neutrophils. *Br J Pharmacol* 1994; **113**: 945–953.
3 Ikeya Y, Taguchi H, Yosioka I, Kobayashi H. The constituents of Schizandra chinensis Baill. I. Isolation and structure determination of five new lignans, gomisin A, B, C, F and G, and the absolute structure of schizandrin. *Chem Pharm Bull* 1979; **27**: 1383–1394.
4 Park JY, Shin HK, Choi YW, Lee YJ, Bae SS, Han J, Kim CD. Gomisin A induces Ca2 + -dependent activation of eNOS in human coronary artery endothelial cells. *J Ethnopharmacol* 2009; **125**: 291–296.
5 Park JY, Yun JW, Choi YW, Bae JU, Seo KW, Lee SJ, Park SY, Hong KW, Kim CD. Antihypertensive effect of gomisin A from *Schisandra chinensis* on angiotensin II-induced hypertension via preservation of nitric oxide bioavailability. *Hypertens Res* 2012; **35**: 928–934.
6 Park JY, Lee SJ, Yun MR, Seo KW, Bae SS, Park JW, Lee YJ, Shin WJ, Choi YW, Kim CD. Gomisin A from Schisandra chinensis induces endothelium-dependent and direct relaxation in rat thoracic aorta. *Planta Med* 2007; **73**: 1537–1542.
7 Seok YM, Choi YW, Kim GD, Kim HY, Takuwa Y, Kim IK. Effects of gomisin A on vascular contraction in rat aortic rings. *Naunyn Schmiedebergs Arch Pharmacol* 2011; **383**: 45–56.
8 Huang XC, Sumners C, Richards EM. Angiotensin II stimulates protein phosphatase 2A activity in cultured neuronal cells via type 2 receptors in a pertussis toxin sensitive fashion. *Adv Exp Med Biol* 1996; **396**: 209–215.
9 Huang XC, Richards EM, Sumners C. Angiotensin II type 2 receptor-mediated stimulation of protein phosphatase 2A in rat hypothalamic/brainstem neuronal cocultures. *J Neurochem* 1995; **65**: 2131–2137.
10 Watanabe T, Barker TA, Berk BC. Angiotensin II and the endothelium: diverse signals and effects. *Hypertension* 2005; **45**: 163–169.
11 Thai H, Wollmuth J, Goldman S, Gaballa M. Angiotensin subtype 1 receptor (AT1) blockade improves vasorelaxation in heart failure by up-regulation of endothelial nitric-oxide synthase via activation of the AT2 receptor. *J Pharmacol Exp Ther* 2003; **307**: 1171–1178.
12 Yayama K, Hiyoshi H, Imazu D, Okamoto H. Angiotensin II stimulates endothelial NO synthase phosphorylation in thoracic aorta of mice with abdominal aortic banding via type 2 receptor. *Hypertension* 2006; **48**: 958–964.
13 Fu M, Xu S, Zhang J, Pang Y, Liu N, Su J, Tang C. Involvement of calcineurin in angiotensin II-induced cardiomyocyte hypertrophy and cardiac fibroblast hyperplasia of rats. *Heart Vessels* 1999; **14**: 283–288.