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Perspective

Ginsenoside Rg1 Acts as a Glucocorticoid Receptor Ligand to Mediate Vasodilation through Nitric Oxide-cGMP Pathway

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Perspective

Coronary Heart Disease (CHD) is the major cause of morbidity and mortality throughout the world [1]. Angina pectoris is caused by coronary blood flow that is insufficient to meet the oxygen demands of myocardium, leading to ischemia. Angina is present symptomatically in about 18% of CHD. Organic nitrates (and nitrites) have been widely used to alleviate or prevent angina pectoris for nearly one century. Nitroglycerin remains the mainstay of angina pectoris relief despite of its adverse effects and tolerance [2-6]. In Traditional Chinese Medicine, ginsenosides are used to relieve angina in CHD patients. Hundreds of randomized controlled trials(RCTs) reported claimed that ginsenoside formulas could relieve the symptoms of CHD, a meta-analysis of 18 eligible RCTs demonstrates moderate evidence that ginsenosides formulas are more effective that nitrates for angina patients [7]. Among the various ginsenosides extracted from ginseng, which component accounts for effects of ginsenoside formulas in relieving angina?

Asianginseng (*Panax ginseng* C.A.Meer) and Americanginseng (*Panax quinquefolius* L.) are the two most recognized ginseng botanicals around the world [8]. In both Asian ginseng and American ginseng, ginsenosides are the major active components [9]. Minor components include amino acid, peptides, and minerals. Ginsenosides are classified into two categories based on presence or absence of a carboxyl group at the C-6 position: protopanaxadiols (Rb1, Rb2, Rc and Rd) and protopanaxatriols (Rg1, Rg2, Re and Rf) [10]. Ginsenosides (except Ro) belong to a family of steroids named steroidal saponins [11,12]. Ginsenosides posses the four *trans*-ring rigid steroid skeleton, with a modified side chain at C-20.The classical steroid hormones have a truncated side chain or no side chain. Many steroids have a β-OH group at C-3; ginsenosides usually have a sugar residue attached to the same site. Ginsenoside Rg1 is among the most abundant and active ingredients in *panax ginseng*, it composed about 0.38% in root of *panax ginseng* [13]. Its molecular formula is $C_{42}H_{72}O_{14}$; molecular weight is 801.01268.

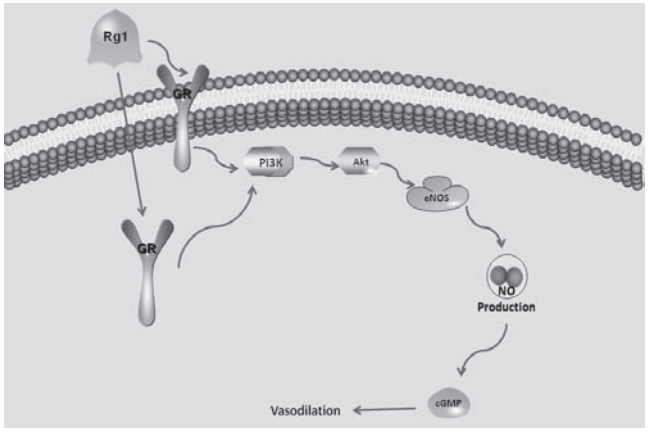

Figure 1: Signal pathway of Ginsenoside Rg1 in vasodilation.

The close connection between NO and ginsenoside Rg1 has increasingly been noted in recent years. Ginsenoside Rg1 has been demonstrated to trigger transcriptional activation of a glucocorticoid response element (GRE)-containing reporter gene, raising the possibility that Rg1 may activate the glucocorticoid receptor [14,15]. Rg1 competed for dexamethasone binding to glucocorticoid receptor with specific affinity and activated a GRE-containing luciferase reporter gene, suggested Rg1 is a functional ligand of glucocorticoid receptor [16]. Rg1 was presented to stimulate the NO formation in endothelial cells which accounts for the endothelium-dependent relaxation and production of cGMP in rat aorta [17]. In other studies, Glucocorticoids have been reported to activate the phosphatidylinositol-3 kinase (PI3K)/Akt pathway after binding to the glucocorticoid receptor [18]. The activated PI3K/Akt pathways leads to phosphorylation of endothelial nitric oxide synthase (eNOS) and increases the production of NO [19]. Rg1 could increase the phosphorylation of glucocorticoid receptor, PI3K, Akt/protein kinase B and eNOS leading to increase NO in human umbilical vein endothelial cell [20]. Rg1 induced endothelial-dependent vessel dilatation through the activation of NO by modulating the PI3K/Akt/eNOS pathway and L-arginine transport in endothelial cells [21]. The schematic signaling pathway of Rg1-mediated vasodilation was illustrated as figure 1. Animal studies showed Rg1 could reduce infarct volume in rat acute myocardial ischemia and infarction models [22]. Rg1 also resisted elevation of ECG T wave and ST segment on acute myocardial ischemia in guinea pigs.

Ginseng extract or ginsenoside formula occupied almost 70% of total Traditional Chinese Medicine used in the treatment of acute angina attack. When they are administrated by sublingual route, the effects can be achieved within several minutes. Rg1 may mediate

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vasodilation through nitric oxide (NO)-cGMP pathway, increase blood supply to the heart muscle, and therefore alleviate angina pectoris. Ginsenoside Rg1 may have promising therapy perspective in the treatment of angina pectoris patients.

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