

**MOLECULAR MECHANISMS INVOLVED IN ACUTE AND CHRONIC EFFECTS OF EPIGALLOCATECHIN GALLATE (EGCG), A GREEN TEA POLYPHENOL, ON VASCULAR FUNCTION OF SPONTANEOUSLY HYPERTENSIVE RATS (SHR)**

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We recently demonstrated that *in vivo* treatment with EGCG, a bioactive polyphenol that makes up the majority of green tea dry mass, improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial ischemia/reperfusion injury in SHR rats (1). In the present work, we investigated molecular mechanisms involved in acute and chronic vascular actions of EGCG. In acute studies, mesenteric vascular vessels (MVB) isolated from 12-wk old SHR and age-matched normotensive WKY were pre-constricted with norepinephrine (NE, 3  $\mu$ M) to a perfusion pressure of ~120 mmHg and then exposed to a submaximal dose of the vasodilator ACh to verify endothelial integrity. Subsequently, MVB were perfused with increasing concentrations of EGCG (1 - 100  $\mu$ M) resulting in a rapid, reversible, and dose-dependent vasodilation. Pre-treatment of vessels with L-NAME (NOS inhibitor, 100  $\mu$ M/20 min) significantly reduced vasorelaxation in response to either ACh or EGCG in both groups ( $p < 0.001$ ). When wortmannin (PI 3-kinase inhibitor; 100 nM/20 min), or PP2 (Src family kinase inhibitor; 10  $\mu$ M/20 min) were added to the perfusate, normal vasorelaxation in response to ACh was observed while the vasodilator response to EGCG was abrogated ( $p > 0.4$ ;  $p < 0.001$ , respectively). In chronic studies, 9-wk old SHR were treated by gavage for 3 weeks with vehicle, EGCG (200 mg/kg/d), or EGCG plus L-NAME (80 mg/L in drinking water). 9-week old WKY controls were given vehicle alone. EGCG therapy significantly lowered systolic blood pressure (SBP) in SHR, but not in SHR given L-NAME ( $p < 0.005$  vs untreated SHR). A significant increase in the total content of Akt and eNOS proteins was detected by WB analysis in MVB homogenates (but not in the aortas) from SHR treated with EGCG when compared to untreated SHR ( $p < 0.001$ ). Concomitant administration of L-NAME did not alter the increased expression of Akt and eNOS in SHR treated with EGCG. In summary: 1. EGCG has acute vasorelaxant effects to stimulate production of NO from endothelium. 2. Vasodilation to EGCG is dependent on activation of Src/PI 3-kinase/Akt/eNOS pathways. 3. Chronic exposure to EGCG increases total content of Akt and eNOS on resistant vessels of SHR rats. We conclude that increased expression of signaling proteins related to production of NO may be one mechanism involved in reduction of blood pressure that we observed in SHR treated with EGCG.

1. Potenza MA, Marasciulo FL, Tarquinio M, Tiravanti E, Colantuono G, Federici A, Kim JA, Quon MJ, Montagnani M. (2007) *Am J Physiol Endocrinol Metab.*, Jan 16 [Epub ahead of print].