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Green Tea May be Benefit to the Therapy of Atrial Fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. Systemic inflammatory state, oxidative stress injury, and atrial fibrosis are identified as the main mechanisms for AF. Considering the multifactorial mechanisms of AF, a novel therapeutic agent with multi-bioactivities should be presented. Regular consumption of green tea has been associated with a reduced risk of coronary heart disease and against a large number of pathologic conditions. Recent results indicate that green tea extract, especially (-)-epigallocatechin-3-gallate, could effectively decrease inflammatory factors secretion, antagonize oxidation, and inhibit matrix metalloproteinase activities. Inhibition of inflammation, modulation of oxidative stress, and targeting tissue fibrosis represent new approaches in tackling AF; therefore, green tea may be an innovative therapeutic candidate to prevent the occurrence, maintenance, and recurrence of AF. J. Cell. Biochem. 112: 1709–1712, 2011.

KEY WORDS: INFLAMMATION; OXIDATIVE STRESS; FIBROSIS; ATRIAL FIBRILLATION; GREEN TEA

Atrial fibrillation (AF) has a high morbidity, mortality and disability, and serious impact on quality of life. Conventional antiarrhythmic drug approaches have limited effectiveness and are associated with risks of serious complications. Structural remodeling has been observed in both clinical and experimental AF paradigms, and is an important feature of the AF substrate. The precise mechanisms underling AF are not fully elucidated, but recent investigations have provided valuable insights that inflammatory conditions and oxidative stress play a significant role in the pathological process. A better understanding of the mechanisms of AF will be benefit for identifying new therapies for preventing AF.

Recently, green tea has received considerable attention for a positive correlation between its consumption and cardiovascular health. Tea leaves are a rich source of extractable polyphenols, commonly referred to catechins. The major polyphenolic compounds in catechins, especially (-)-epigallocatechin-3-gallate (EGCg) [Astill et al., 2001; Yao et al., 2005; Friedman et al., 2005], exert vascular protective effects through multiple mechanisms, including anti-inflammatory, anti-oxidative [Balentine et al., 1997], and inhibiting the gelatinolytic activity of MMPs [Demeule et al., 2000; Maeda et al., 2003]. Although many studies have demonstrated that green tea has powerful protective effect against cardiovascular disease, whether it has effect on AF is still poorly unknown. Accumulating evidences have elucidated that catechins can downregulate of the inflammatory response and anti-oxidative activities through inhibition of synthesis and release of pro-inflammatory mediators, scavenging free radicals, inhibiting accumulation of fibrillar collagen deposits, or inhibiting transcription factors such as nuclear factor κB(NF-κB). Hence, we hypothesize that green tea could serve as a novel therapeutic compound in managing AF.

EFFECT OF GREEN TEA ON THE INFLAMMATORY STATE IN ATRIAL FIBRILLATION

Much attention has been devoted in the past few years to assess the role of inflammation in AF. The contribution of the inflammatory cascade to the onset of AF is suggested by the high incidence of AF in postoperative cardiac surgeries, a state of intense inflammatory process [Bruins et al., 1997; Ommen et al., 1997; Gabay and Kushner, 1999]. The frequent occurrence of AF in patients with inflammatory conditions such as myocarditis and pericarditis has raised the possibility that AF is associated with local inflammation [Spodick,

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1976; Morgera et al., 1992]. Further evidences on this issue have come from the increase in inflammatory markers such as C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), and interleukin-6 in both paroxysmal and persistent AF, compared to control subjects.[Chung et al., 2001; Dernellis and Panaretou, 2001; Aviles et al., 2003; Blake and Ridker, 2003; Conway et al., 2004; Sata et al., 2004; Psychari et al., 2005] Moreover, longer duration of AF has been found to be associated with higher hs-CRP levels compared with shorter duration of AF, which indicates that there is a link between AF burden and systemic inflammation [Chung et al., 2001; Watanabe et al., 2005].

Cytokines are produced by activated cells, usually monocytes and macrophages, they are paramount in activating the inflammatory cascade and in the production of acute-phase proteins, such as CRP. Among the molecules involved in inflammation, nuclear factor κB (NF-κB) is a key upstream regulator, which also is a key transcription regulator, coupling redox state to alterations in gene transcriptional regulation in such states as injury and inflammation stress [Dudley et al., 2005], so it seems possible that NF-κB may mediate the pathogenesis of AF. NF-κB is associated with the cytoplasmic inhibitory protein IκBα in inactive form [Gerritsen et al., 1997]. Cellular stimulation with NF-κB agonists results in the phosphorylation and degradation of IκBα, allowing the p50/65 heterodimers of NF-κB to translocate to nucleus and initiate expression of target genes [Read et al., 1994; Brown et al., 1995; Ouchi et al., 2000]. A recent study by Aneja et al. [2004] observed administration of EGCg during myocardial ischemia reperfusion significantly decreased IκB kinase activity, resulting in the reduction of IκBα degradation and NF-κB activity. In addition, EGCg can directly inhibit the phosphorylation of IκB, thereby preventing NF-κB translocation to the nucleus [Nomura et al., 2000]. In consistent with these results, Suzuki et al. [2006] reported a decreased activity of NF-κB in murine cardiac transplants after oral administration of green tea polyphenols (20 mg/kg/day) for 60 days.

As discussed above, EGCg as one of the major and the most active components of green tea, has been shown to have protective effect to inflammatory state in AF through inhibit the phosphorylation of IκB, suppression of NF-κB activity and decrease circulation IL-6, CRP, and hs-CRP.

EFFECT OF GREEN TEA ON THE OXIDATIVE STRESS IN ATRIAL FIBRILLATION

Emerging evidences implicate that oxidative stress and inflammation are relevant players in atrial structural remodeling. Inflammatory cell infiltration and calcium overload during high atrial rate may promote oxidative damage in atrial tissue which promotes atrial fibrosis and facilitates AF continuation. Ramlawi et al. [2007] have reported that patients who exhibit postoperative atrial fibrillation (PAF) after cardiac surgery have significantly increased acute oxidative stress with an elevation in total peroxide levels in serum, which translates into increased myocardial oxidation.

Carnes et al. have shown that AF induced by rapid pacing in dogs decreases tissue ascorbate levels and increases protein nitration, a marker of oxidative and nitrosative stress. Biochemical evidence of oxidation by peroxynitrite and hydroxyl radicals, both downstream products of oxygen radical generation, has also been demonstrated in experimental models of AF [Mihm et al., 2001]. Examination of gene transcriptional profiles of human atrial tissue of AF patients showed a shift toward the pro-oxidative gene expression [Kim et al., 2003]. The main contributors to atrial oxidative stress were myocardial NADPH-oxidase and uncoupled NO synthase [Kim et al., 2005]. Together, these findings suggest the presence of a causal relationship between pro-oxidative cellular redox state and AF.

Tea catechins have been largely studied for their anti-oxidantive capacities and considered as important antioxidants. Due to the number and arrangement of the phenolic hydroxyl groups, catechins are excellent electron donors and efficient scavengers of free radicals such as superoxide anions, singlet oxygen, nitric oxide, and peroxynitrite [Jovanovic and Simic, 2000; Paquay et al., 2000]. Nishikawa et al. [2007] reported that EGCg inhibited cytosolic subunits of NADPH oxidase from translocating into membrane suggesting inhibition of NADPH oxidase activity in cutaneous mastocytoma cells. Catechins may also reduce the oxidative stress by modulating the reactive oxygen species generating enzymes such as inducible NO synthase (iNOS). Agnetti et al. [2005] also evaluated that green tea extract (GTE) supplementation counteracted on iNOS induction and activity in cardiomyocytes. Chan et al. [1997] investigated that EGCg may reduces NO production by two mechanisms: reduction of inducible nitric oxide synthase gene expression and inhibition of enzyme activity. Being able to reduce NO production at both iNOS mRNA accumulation and enzyme activity, EGCg will provide a distinctive advantage as a novel antioxidant agent.

Since AF has been shown to be associated with oxidative stress, the question of whether antioxidant agents could decrease AF rates has been raised. Interestingly, administration of the antioxidant ascorbate attenuated atrial peroxynitrite formation and electrophysiological remodeling in a canine model of rapid atrial pacing [Carnes et al., 2001]. Similarly, statins have been shown recently to reduce angiotensin II-stimulated (but not basal) NAD(P)H oxidase activity in human right atrial appendage [Maack et al., 2003] and to attenuate effective refractory period reduction and AF inducibility in dogs exposed to rapid atrial pacing [Shiroshita-Takeshita et al., 2004]. Therefore, green tea like other antioxidant agent is proposed to be a dietary supplement in the prevention of AF.

EFFECT OF GREEN TEA ON THE TISSUE FIBROSIS IN ATRIAL FIBRILLATION

Although tachycardia-induced electrical remodeling creating a substrate for persistent AF, led to the concept that "Atrial Fibrillation Begets Atrial Fibrillation" [Wijffels et al., 1995], the subsequent structural remodeling plays an important role in progressing sustained AF, producing fibrosis that alters atrial tissue composition and function. Tissue fibrosis results from an accumulation of fibrillar collagen deposits, which has been documented in lone-AF patients compared with sinus rhythm control subjects [Frustaci et al., 1997]. Pathologically produced

collagen differs from that in normal myocardium, with altered ratios of collagen subtypes [Xu et al., 2004; Grammer et al., 2005]. Dense and disorganized collagen weave fibrils physically separate remaining myocytes [Rossi, 1998], and can create a barrier to impulse propagation. Meanwhile studies by Xu et al. reported that the increased level of collagen I associated with selective down regulation of TIMP-2, along with up regulation of MMP-2 expression and activity in atrium, correlates with left atrial dimension and the maintenance and recurrence of AF in end-stage heart failure. Additionally, a striking increase in both abundance and activity of atrium MMP-2 and MMP-9 in patients with permanent AF suggests the importance of these two gelatinases not only in the ECM remodeling of the failing heart but also in the development of sustained AF.

There is considerable evidence demonstrating the inhibitory effect on MMP-2 and MMP-9 caused by EGCg which was confirmed by gelatin zymography and was observed with both various rat tissues and human brain tumors [Demeule et al., 2000]. Moreover, studies by El Bedoui et al. [2005] reported that EGCg prevents MMP-2 expression and its activation via the direct inhibition of the physiological activator of MMP-2 in vascular smooth muscle cells (VSMCs). In addition, EGCG prevented TNFa-induced expression of matrix metalloproteinase-9 (MMP-9) in VSMC [Kim and Moon, 2005]. Cheng et al. [2003] investigated that EGCg forms a reversible complex with MMP-2, resulting in the inhibition of gelatinolytic activity of MMP-2.

The above evidence suggests that EGCg may have the favorable effect on AF occurrence might be because of its ability to inhibit the expression and activity of MMP-2 and MMP-9 which subsequently ameliorate tissue fibrosis by collagen deposition.

THERAPEUTIC EFFECT OF GREEN TEA ON ATRIAL FIBRILLATION

EGCg has strong effect of inhibiting overproduction of inflammatory cytokines and mediators, meanwhile it may also reduce the oxidative stress by inhibiting of NADPH oxidase activity and modulating the ROS generating enzymes such as iNOS, so that green tea could be regarded as a promising drug of blocking the the initiation and progress of inflammation and oxidation in AF. Furthermore, EGCg can inhibit the gelatinolytic activity of MMP-2 and MMP-9, subsequently ameliorate structural remodeling of tissue fibrosis by reducing collagen deposition, acting as an effective anti-fibrotic agent in the myocardium. Therefore, green tea may be a therapeutic modality for AF.

CONCLUDING REMARKS

The above discussion suggests that green tea may have a useful therapeutic effect in AF through their anti-inflammatory, anti-oxidative, and attenuation of atrial structural remodeling. Current evidences suggest that the protective effect of green tea on cardiovascular disease mainly contribute to its catechins, especially EGCg. Meanwhile, other catechins of green tea whether have similar effects on inflammatory response and oxidative stress are still uncertain. More detailed and profound analysis of molecular actions in myocardium is necessary before safe clinical use of tea polyphenols will become possible for treatment of AF.

Though there is still no document to illustrate the function of green tea in AF. In this prospect, we attempt to correlate its functional effects to molecular signal transductive pathways and focus on molecular targets of naturally occurring compounds of green tea in the management of AF by inhibiting the activation of transcription factors, cytokines, and key enzymes reaction.

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