Protective effect of caffeic acid phenethyl ester on myocardial injury due to anti-oxidant action

Caffeic acid phenethyl ester (CAPE) is an important active component of propolis (a honey-bee hive extract). Propolis contains >300 active constituents, with flavonoids, phenolic acids, phenolic acid esters, terpenoids, steroids and amino acids being among the main components (1).

Caffeic acid phenethyl ester was first chemically synthesized at Columbia University in 1988 (2), and was subsequently considered to be a potent anti-cancer component of propolis (3), as well as being a potent anti-inflammatory and anti-oxidant agent. The interaction of these 2 main properties with other molecular actions of CAPE means that it possesses a plethora of important biological activities. CAPE showed promising efficacy in both in vitro and in vivo studies of animal models, with minimum adverse effects, its effectiveness being demonstrated in multiple target organs. It also has neuroprotective, hepatoprotective and cardioprotective properties. Cardio protective properties of CAPE have been reported both in vitro and in vivo studies, including attenuation of cardiomyocyte apoptosis, antiarrhythmic activity, reducing myocardial infarction (MI) size, and having anti-oxidant properties (4).

These findings suggest a cardioprotective propensity of CAPE, especially in relation to its antioxidant property. However, no one has explored the effects of both NG-Nitro-L-arginine (L-NNA) and CAPE on cardiac tissue in terms of the resultant histopathology.

As mentioned above, İlhan et al. (5) published in this issue of Anatolian Journal of Cardiology investigated the effects of CAPE on hypertensive rats induced by L-NNA with isoproterenol (ISO)-induced myocardial injury. Systolic blood pressure (SBP) in the L-NNA-treated groups was increased by the 7th day, but earlier studies indicated that the effects of CAPE on SBP were controversial. Parlakpınar et al. (6) found that CAPE administration had no significant effect on hemodynamic parameters (heart rate, SBP) during ischemia or reperfusion in male Wistar rats. However, Iraz et al. (7) reported that CAPE had a transient hypotensive effect via a central parasympathetic control mechanism on heart rate in male Sprague-Dawley rats. On the other hand, Long et al. (8) found that CAPE had a vasorelaxant effect on porcine coronary artery ring segments by inducing NO and adrenergic beta-receptors.

The study presented on this issue proved that CAPE reduced the blood pressure slightly in hypertension induced in rats by L-NNA with or without ISO-induced myocardial damage (5). The difference between present and previous studies is that CAPE was given to animals over a subacute period (7 days), whereas it was given acutely in previous studies. Furthermore, we show that CAPE improves the level of NO that falls in the rat hearts after ISO administration. İlhan et al. (5) infer that the slight hypotensive effect of the agent will be balanced in this subacute period and CAPE can act as positive inotropic agent by inducing beta-adrenoceptors and dilating coronary arteries, and inducing NO without affecting blood pressure. This study provides a new viewpoint that CAPE might be useful in both hypertensive and normotensive patients with a heart attack.

Furthermore, İlhan et al. (5) proved that AST and LDH levels in L-NNA+ISO group are significantly increased compared to control group. ISO also caused extensive necrosis and mononuclear cell infiltration in hypertensive rat myocardium. CAPE reversed the enhanced AST and LDH levels, as well as the extensive necrosis and the mononuclear cell infiltration in L-NNA+ISO+CAPE group compared with LNNA+ISO. Their findings suggest that CAPE might be preferred as an agent to protect the hypertensive myocardium from injury induced by isoproterenol which induces antioxidant enzymes and inhibits lipid peroxidation.

Oxidative stress is defined as a tissue injury due to an imbalance between the production of reactive oxygen species (ROS) and endogenous antioxidant defense systems. Under these circumstances, endogenous antioxidants (catalase, superoxide dismutase, glutathione and cytochrome-c-oxidase) may be unable to counter ROS generation. Thus their presence could cause cell damage by peroxidation of membrane lipids, sulphydryl enzyme inactivation, protein crosslinking and DNA breakdown (9).

Caffeic acid phenethyl ester can affect ROS production and ROS can activate extracellular signal-regulated kinases (ERKs), as well as stress-responsive mitogen-activated protein kinases (SR-MAPKs), p38-kinases and c-jun N-terminal kinase (JNKs) in both cardiac myocytes and fibroblasts (10, 11). Activation of ERKs could lead to phosphorylation and degradation of IkB, allowing nuclear translocation of NFkB. Many promoters of MMP (pMMP) have NFkB binding sites, leading to increased transcription (12).

Caffeic acid phenethyl ester is curative when it was administered in MI, as evidenced by a marked reduction in the area of damage and cardiomyocyte injury parameters (LDH, CK-MB and

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Accepted Date: 12.07.2014 **Available Online Date:** 22.08.2014

DOI:10.5152/akd.2014.124317

troponin I). The proposed mechanism is seen as an attenuation of cardiomyocyte apoptosis by CAPE inhibiting p38 MAPK activation and caspase-3 activity, along with reduction of the pro-inflammatory cytokines, IL-1b and TNF-a, in cardiac tissues. The free radical scavenging activity of CAPE is also involved in preventing apoptosis in ischemia/reperfusion (6).

Caffeic acid phenethyl ester has not yet been investigated as a protective agent or a potential therapeutic agent in humans. Investigation of its efficacy in clinical trials is strongly needed to establish any therapeutic benefit for different human diseases after full preclinical toxicological studies have taken place and given more insight into its pharmacokinetics.

CAPA (caffeic acid phenethyl amide, N-trans-caffeoyl-β-phenethylamine), a CAPE analog, synthesized from 3,4-methylene-dioxy-cinnamic acid, with an amide linkage between caffeic acid and the phenethyl group that resist hydrolysis within the circulation, is more stable than CAPE in rat plasma. This gives it a significantly longer half-life in the systemic circulation than CAPE after i.v. administration to male rats. It exerts beneficial effects against diet- and STZ-induced metabolic changes, decreases the size of MI after global ischemia/refusion by increasing coronary flow, and mitigates cardiac dysfunction in abdominal aortic banding-induced ventricular hypertrophy (13, 14). According to these studies, CAPA may have a future as a beneficial agent in the treatment of cardiovascular disease.

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