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AMELIORATIVE EFFECT OF BLACK TEA ON NICOTINE INDUCED CARDIOVASCULAR PATHOGENESIS IN RAT

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ABSTRACT

Regarding the role of nicotine in the development of cardiovascular complications of smoking, we investigated whether black tea has a modulatory effect on cardiovascular pathogenesis of nicotine in rat. Animals were randomized to control, tea, nicotine and tea plus nicotine groups. Test groups received black tea brewed (adding 400 ml boiling water to 10 g Lipton black tea for 5 min) orally alone or with nicotine 2 mg/kg/day, s.c. separately or combined for four weeks. On 28th day, lipids profile of blood and also malondialdehyde (MDA) level, glutathione peroxidase (GPx) activity and total antioxidant capacity (TAC) of heart tissue were measured. Nicotine administration caused a significant increase in total cholesterol, TG and HDL-C and also atherogenic index of plasma (log TG/HDL-C). Moreover, nicotine increased MDA level of heart. Black tea alone increased the antioxidant capacity of heart tissue without significant effect on lipid profile and MDA levels. Concomitant use of black tea and nicotine significantly attenuated the hyperlipidemic and atherogenic effects of nicotine but was unable to attenuate the MDA. Our findings suggest that black tea consumption reduces hyperlipidemia and atherogenesis as two cardiovascular risk factors and complications of nicotine, in rat. If these results can be extrapolated to human, smokers who daily drink black tea may be less at risk of cardiovascular disease.

Keywords: Nicotine, black tea, atherogenic index, blood lipids, total antioxidant capacity, heart

INTRODUCTION

Cardiovascular diseases (CVDs) are the most common cause of death as currently they account for about 30 percents of deaths' worldwide, nearly 40 percent in high-income countries and roughly 28 percent in low- and middle- income countries (Zipes et al., 2008). Epidemiological studies indicate high correlations between mortality rates and three major CVD risk factors; smoking, serum cholesterol, and hypertension (Kuulasmaa et al., 2000). Nicotine is one of the 4,000 or more chemical components of cigarette smoke, and many harmful effects of smoking such as cardiovascular diseases are attributed to this substance (Benowitz, 1998).

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Previous experiments indicated that exposure to nicotine increases the plasma lipid levels (Chattopadhyay and Chattopadhyay, 2008), tissue lipids (Norioko et al., 1981) and it also accelerates the lipid peroxidation in rat (Ashakumary and Vijayammal., 1996). It is believed that nicotine triggers reactive oxygen species (ROS) generation (Yildiz et al., 1998). ROS in turn can induce oxidative stress and activate the lipid peroxidation process (Kovacic and Cooksy, 2005) that finally leads to cellular damage. Sudheer et al. (2005) have shown that chronic nicotine administration is associated with circulation prooxidant/antioxidant imbalance. On the other hand, some experiments documented that at least a part of neuroprotective effect of nicotine against Parkinson's and Alzheimer's diseases is due to antioxidant properties of this substance (Linert et al., 1999; Túnez et al., 2004).

Some natural compounds, including the flavonoids, have antioxidant properties. Black tea is one of the most common beverages and makes up about 75 % of world tea consumption (Krishnan and Maru, 2006). Cardiovascular protective effect of black tea has been demonstrated in some previous studies (Geleijnse et al., 2002; Joukar et al., 2012; Duffy et al., 2001). Tea contains considerable amounts of flavonoids that its cardioprotective effect is attributed to these compounds (Geleijnse et al., 2002). Behavioral studies have shown that cigarette smokers, compared to non-smokers, consume more tea and coffee (Golding et al., 1983; Dunn and Thomas, 1973). However, the interaction of tea and nicotine in combine on cardiovascular system performance has been less noted. In a previous study we showed that administration of black tea or nicotine for a period of 4 weeks may have a mild cardioprotective effect as confirmed by reduction of myocardial damage in stressful conditions. However, concomitant use of these materials was unable to enhance this beneficial effect (Joukar et al., 2012).

In the present study, to clarify whether black tea has a positive or negative influence on the nicotine induced cardiovascular pathogenesis, we focused and tested the effect of subchronic administration of black tea and nicotine, alone or in combination, on the plasma lipids profile, lipid peroxidation index and heart tissue antioxidant level of rats.

MATERIALS AND METHODS

Chemicals

Nicotine was purchased from Sigma, UK and sodium thiopental was purchased from Sandoz, Austria. Black tea was from Lipton, Inc., UK.

Animal groups and experimental protocol

All empirical procedures, harmonizing to the national guidelines for conducting animal studies (Ethic committee permission No 86/123KA—Kerman University of Medical Sciences, Kerman, Iran) and were performed on male Wistar rats aged 3 months and weighed 250–350 g with appropriate implementation of animals care principles and received the same regular diet during the study. The animals were divided randomly into 4 groups (n=12 in each group) including control group (CTL), tea group (T), nicotine group (N) and black tea plus nicotine group (N+T). Tea group consumed black tea brewed as their sole source of liquid for four weeks (Joukar et al., 2012; Yoxall et al., 2005). Black tea brewed prepared daily by adding 400 ml boiling water to 10 g Lipton tea (five bags) in a flask. The bags were removed after five minutes, and the drink was allowed to cool for use (Joukar et al., 2012). The average volume consumption of tea brewed by each rat was 34 ± 5 ml/day. Nicotine group was treated with nicotine 2 mg/kg/day (s.c.) for four weeks (Joukar et al., 2012; Luo et al., 2006). Tea+nicotine group received tea along with nicotine with the same doses in tea and nicotine groups. In addition, normal saline (0.5 ml) as the vehicle of nicotine was injected daily to CTL and tea groups during the experiment. On day 29, under deep anesthesia by sodium thiopental (50 mg/kg i.p.), blood sample was taken

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and centrifuged for plasma separation. Total cholesterol, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C) and triglyceride (TG) levels were measured by routine laboratory methods. The atherogenic index of plasma, as a marker of plasma atherogenicity, was calculated as Log (TG/HDL-C) (Tan et al., 2004; Dobiásová and Frohlich, 2001). At the end of experiments, animals were killed; the hearts were excised and washed with cold saline. A piece of heart apex dissected, weighted and homogenized in 5 ml of 0.1 MTris–HCl buffer (pH 7.4) in ice-cold condition. After centrifuging, the clear supernatant solution was taken for the biochemical analysis. Total proteins were measured by using the Lowry et al. method (Lowry et al., 1951). Malondialdehyde (MDA) levels, as an index of lipid peroxidation which produced by oxidative elements activation, were estimated by concentration of thiobarbituric acid reactive substances (TBARS) in heart tissue (Ohkawa et al., 1979). Total antioxidant capacity and glutathione peroxidase (GPx) activity of heart tissues were determined using their relative Randox assay kits, respectively (according to the manufacturer's protocol) (Koch et al., 2002; Joukar et al., 2010).

Statistical analysis

The results were presented as mean ± S.E.M. The data were analyzed by One-Way ANOVA followed by LSD multiple comparison post hoc test and P-value ≤ 0.05 was considered as statistically significant.

RESULTS

On day 29, the weight gain of control group versus other groups was statistically significant ($p<0.01$). The control group showed 32 % weight gain, while the weight gain of tea, nicotine and N+T groups were only 2 %, 5 % and 2.7 %, respectively.

Lipids profile

Four weeks consumption of black tea as a sole source of liquid had no significant effect on plasma lipids profile of animals. While, alone nicotine administration was associated with increasing plasma levels of TG in comparison with control and tea groups ($p\leq0.01$). When animals used black tea along with nicotine, the TG levels decreased significantly ($p\leq0.01$), as there was no significant difference with result of the control group. On the other hand, separately or combined use of black tea and nicotine lead to increase of total cholesterol and HDL-C that only were significant in nicotine and N+T groups whenever compared to control group. Interestingly, using of these substances had no remarkable effect on plasma levels of LDL (Table 1).

Table 1: Plasma lipid levels in different animal groups of study

Group	Total Chol (mg/dL)	HDL-C (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	TG (mg/dL)
CTL	45.2±2.6	30.4±1.6	8.4±0.9	6.3±1.1	45.6±3.5
Tea	48.5±1.9	33.1±1.2	7.9±0.6	7.5±0.8	59.2±5.2
Nicotine	51.9±1.9*	35.2±1.2*	7.5±0.5	9.3±6*	76.6±4.2‡
N+T	53.6±1.9*	36.3±1.3§	8.6±0.7	8.7±0.9	55.3±5.1#

Values are means ± SEM. Animal numbers were 12 in each group. CTL: control, Tea: black tea, N+T: nicotine+black tea, Total Chol: total cholesterol, TG: triglyceride, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, HDL-C: high-density lipoprotein. *P < 0.05 and § P < 0.01compared with CTL group, ‡P < 0.01 compared with CTL and tea group, #P < 0.01 compared with Nicotine group.

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Plasma atherogenic index

Plasma atherogenic index that expressed as Log (TG/HDL-C) only significantly elevated in the nicotine group. As seen in N+T group, combination of tea and nicotine reduced this index to normal level (Figure 1).

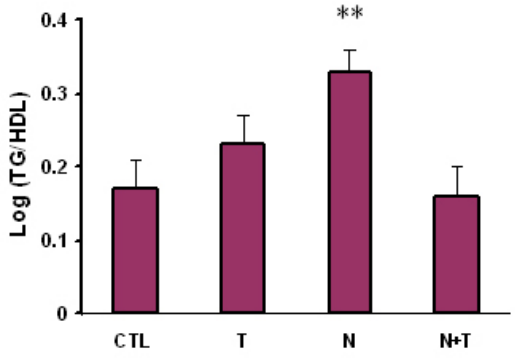

Figure 1: Atherogenic index of plasma in different groups. Values are means ± SEM. n= 12, CTL: control, T: black tea, N: nicotine, N+T: nicotine+black tea, HDL-C: high-density lipoprotein, TG: triglyceride. **P < 0.01 versus CTL and N+T groups

Antioxidant indices

Total antioxidant capacity (TAC) of heart increased significantly in tea group versus control group (P<0.05). Administration of nicotine was associated with a non-significant reduction of this parameter. However, combination of tea and nicotine improved the TAC to the level of CTL group (Figure 2).

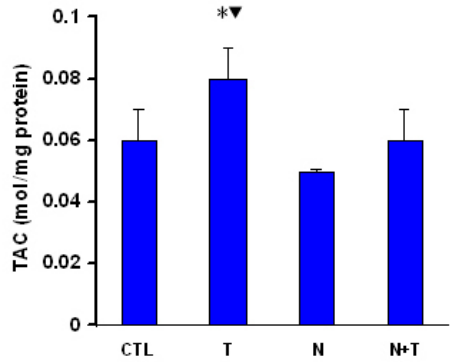

Figure 2: Total antioxidant capacity (TAC) of heart tissue. Values are means ± SEM. n= 6-7, CTL: control, T: black tea, N: nicotine, N+T: nicotine+black tea, *P < 0.05 compared with CTL. ▼P < 0.01 compared with nicotine group

GPx activity showed incremental trend in tea or N+T groups but had no significant difference with CTL (Figure 3). The values of MDA were statistically significant in nicotine and N+T groups with respect to CTL group (P< 0.05) (Figure 4).

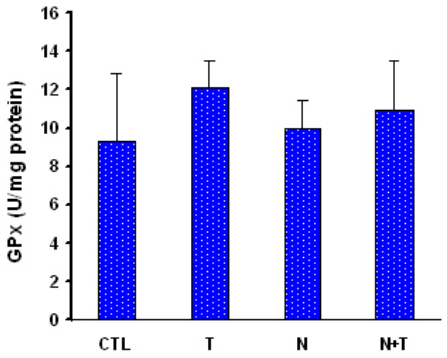

Figure 3: Glutathione peroxidase (GPx) activity of heart tissue. Values are means ± SEM. n= 6-7, CTL: control, T: black tea, N: nicotine, N+T: nicotine+black tea

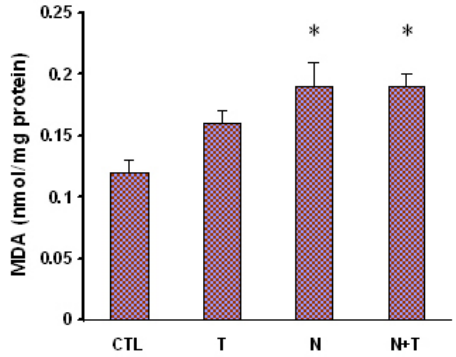

Figure 4: Malondialdehyde (MDA) levels of heart tissue. Values are means ± SEM. n= 6-7, CTL: control, T: black tea, N: nicotine, N+T: nicotine+black tea, *P < 0.05 compared with CTL group

DISCUSSION

Based on some previous findings, it is believed that nicotine is the main component in tobacco smoking causing cardiovascular complications such as atherosclerosis, hypertension, heart attack and stroke. The present study was conducted to assess the consequence of subchronic co-administration of black tea and nicotine on plasma lipids profile and antioxidant levels of heart tissue of rats to estimate the probable modulatory effect of black tea on cardiovascular side effects of nicotine.

Subchronic consumption of black tea and nicotine either alone or in combination was associated with reduction in animals' weight gain significantly. However, concomitant use of these agents has no negative synergism effects on body weight gain. These findings also documented in previous studies, as it is reported that chronic black tea extract (50 g in 800 ml) decreased body weight gain of rats as much as 17.8 % (Hamdaoui et al., 1997). In addition, the negative nicotine effect on body weight gain is reported frequency in literature (Andresen et al., 2008; Bellinger et al., 2010) that all of them confirm our findings.

The results showed also subchronic administration of nicotine, despite its prevention effect on animals weight gain, significantly increased the plasma levels of total cholesterol, TG and HDL-C and also atherogenic index of plasma, but had no effect on plasma LDL-C levels. Moreover, nicotine injection resulted to increasing MDA, as a marker of lipid peroxidation, in heart tissue. On the other hand, black tea alone amplifies the antioxidant capacity of heart tissue, without significant changes in lipid profile and MDA levels of animals. Concomitant use of black tea and nicotine significantly attenuated the hyperlipidemic and atherogenic effects of nicotine but was unable to attenuate the MDA level.

Similar to our findings, in a study, Allen et al. (1994) showed that, in smoking abstinent patients, six weeks transdermal nicotine administration leads to an increase in levels of HDL-C and TG in plasma. Other experiments also indicated increase in TG and total cholesterol followed to nicotine administration but HDL-C reduction was also reported (Chattopadhyay and Chattopadhyay, 2008; Valenca et al., 2008).

The discrepancy in HDL-C result may be due to the different experimental condition, animals' specious and even the dose and period of nicotine administration. In addition, increasing of lipid peroxidation (as the MDA elevation) followed to nicotine administration is reported in other studies (Ashakumary and Vijayammal., 1996; Zhou et al., 2010). These results are consistent with our results.

LDL-C is the key target in treatment of hyperlipidemia. However, many cardiovascular events occur in the presence of normal LDL-C. Previous findings considered a predictive role for low HDL-C and high TG on the incidence cardiovascular events. Gaziano et al. (1997) proposed "the ratio of triglycerides to HDL-C" as a strong predictor of myocardial infarction. Recently, it was shown that hypertriglyceridemia is independently associated with endothelial dysfunction in patients with coronary heart disease during statin therapy and hypertriglyceridemia therapy is recommended in these patients (Yunoki et al., 2011).

Zoppini et al. (2012) indicated that the TG/ HDL-C ratio was associated with an increased incidence of microvascular complications in individuals with type 2 diabetes mellitus. In another human study, the positive correlation between TG/HDL-C and obesity/overweight and metabolic syndrome were reported (Musso et al., 2011). It is believed that hypertriglyceridemia is associated with increased small, dense LDL particles and also amplified cholesteryl ester (CE) mass transfer from HDL-C to apolipoprotein B (apoB)-containing lipoproteins (Guérin et al., 2001). TG has also been proposed to be a major determinant of cholesterol esterification/transfer and HDL-C remodeling in human plasma (Murakami et al., 1995).

According to available information, the increased level of plasma triglyceride as an independent risk factor of cardiovascular disease and Log (TG/HDL-C) as a plasma atherogenic index (Dobiásová and Frohlich, 2001) are important in the cardiovascular pathogenesis. Based on increasing these two parameters, along with rising of lipid peroxidation index (MDA) in nicotine group, one can conclude that cardiovascular disorder is one of the outcomes of nicotine consumption. High plasma TG leads to increasing TG-enriched HDL-C. TG-enriched HDL-C is substrates for hepatic lipase (HL) that hydrolyzes TGs to form small, dense

HDL-C (Barter et al., 2003). Both HL-HDL-C lipolysis and TG-enriched HDL-C increase HDL-C catabolism (Rashid et al., 2002, 2003). Ashakumary and Vijayammal (1997) have reported increase of TG-enriched HDL-C in rats that received nicotine which is consistent with our findings. Furthermore, toxic effect of nicotine may reduce the number of hepatocytes and hence increased lipid metabolism disturbance (Valenca et al., 2008).

Tea usage alone had no significant effect on lipids profile despite its prevention effect on animals weight gain, but was associated with increasing TAC and in some extent, GPx. In agreement with our results, amplification of the antioxidant system by black tea is reported by others (Bhattacharyya et al., 2007; Khan, 2006) and attributed to black tea flavonoids. As shown in the Results' section, when black tea is consumed with nicotine, plasma atherogenic index and TG level significantly decreases and the share of HDL-C in total cholesterol level is increased. It was recently reported that black tea polyphenols attenuated postprandial hypertriacylglycerolemia by decreasing triacylglycerol absorption through the inhibition of pancreatic lipase activity (Kobayashi et al., 2009; Ikeda et al., 2005). Therefore, in our study, plasma TG reduction in T+N group may result from polyphenol induced pancreatic lipase inhibition and hence reduction of TG absorption.

Regarding the oxidant/antioxidant activity, in present study, despite the MDA level elevation in nicotine groups, TAC and GPx did not show significant changes in respect to the control group. This finding raises two possibilities; firstly, antioxidant system of heart tissue similar to brain tissue (Linert et al., 1999; Túnez et al., 2004), may have a different response to nicotine, and secondly, considering to subchronic use of nicotine in the present study, it may have not been enough time for depletion of antioxidant reserves of heart tissue. However significant increases of MDA and non significant decremental trend of heart total antioxidants is a sufficient reason for the increasing lipid peroxidation in presence of nicotine.

Altogether, the antioxidant power of black tea was not significant for improvement of nicotine induced lipid peroxidation in our study. In addition to the above possibilities, dose dependent antioxidant effects of tea (Lee et al., 2005; Gardner et al., 2007) is the other probable reason for inadequacy of tea consumed in this study in reducing MDA in T+N groups, however, to clarify the exact mechanism of these findings need more investigation.

In conclusion, the present study suggests that black tea consumption may protect the cardiovascular system from some deleterious effects of nicotine, including hyperlipidemia and atherogenesis even without remarkable effects on heart antioxidant levels. This may be partly by inhibition of intestinal TG absorption and hence decreasing plasma atherogenic index and also by prevention of nicotine-induced lipid metabolism. If our results can be extrapolated to human, tobacco smokers who daily drink a considerable amount of black tea are less at risk of cardiovascular disease.

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