Department of Pathophysiology[1], School of Medicine, Department of Pharmacology and Toxicology[2], Pharmaceutical Faculty, and Pharmacobiochemical Laboratory[3], Shool of Medicine, Komensky University, Bratislava, Slovak Republic

Passive cigarette smoking induced changes in reactivity of the aorta in rabbits: effect of captopril

F. Simko[1], P. Martinka[2], J. Brassanova[2], J. Klimas[2], A. Gvozdjakova[3], J. Kucharska[3], V. Bada[3], I. Hulin[1] and J. Kyselovic[2]

Besides impairment of myocardial tissue, various vascular alterations were observed after chronic exposure to cigarette smoke. Smoking causes reduction in the compliance of peripheral arteries and impairment of endothelium dependent vasodilatation [1]. These adverse effects of smoking on vessel reactivity can be attenuated by alpha blockers, calcium entry blockers [2] or arginine vasopressin antagonist [3], while data on the potential benefit of angiotensin converting enzyme (ACE) inhibition are scarce. The aim of this work was to investigate the ability of the ACE inhibitor captopril to prevent alterations in reactivity of the aorta caused by passive smoking in rabbits.

Four groups of rabbits were investigated in a three week experiment: control (c) ($n = 8$), control + captopril (cC) ($n = 8$) – 7.5 mg twice daily intramuscularly, passive smoking (s) ($n = 8$) – 3 cigarettes twice daily, and passive smoking + captopril (sC) ($n = 8$) captopril administered as above [4, 5]. The rabbits were male, Chinchilla species, with an average body weight of about 3000 g. All animals were housed in individual cages and fed a regular pellet diet.

The following vasoactive drugs were used: prostaglandin F2α (10^{-5} mol $\cdot$ l^{-1}), potassium chloride (50 mmol $\cdot$ l^{-1}) and acetylcholine. After killing animals a six centimeter long segment of the thoracic aorta was dissected free, and placed in an ice-cold Krebs solution, cleaned of connective tissue and cut into about 4 mm long segments. The individual segments were attached between an isometric force transducer (Sanborn FT 10) and a holder under a tension of 20 mN in a 20 ml organ bath containing Krebs solution. After a resting period of 90 min the contraction of the aorta was observed 30 min after administration of the vasoactive substance. Acetylcholine induced relaxation was used to test the function of the endothelium on the vessel precontracted by norepinephrine (6, 7).

The results are expressed as mean ± S.E.M. Differences between groups were assessed by one way ANOVA test with $p \leq 0.05$ taken as significant.

In the tonic part of aortic contraction, smoking decreased the contractile answer to potassium chloride (the attenuation of contraction to PGF2α was not significant). Captopril restored the contraction of the aorta to potassium chloride and to PGF2α (Fig. 1). The acetylcholine induced relaxation of the aorta was strongly decreased in the passive smoking group. Captopril completly reversed this deterioration of endothelium dependent relaxation of the aorta (Fig. 2).

The most interesting finding was the fact that endothelium dependent relaxation of the aorta was strongly diminished in the passive smoking group. This result is in agreement with findings of other authors. Ota et al. [8] showed that water soluble cigarette smoke extract inhibited endothelium-dependent relaxation of the aorta in a dose dependent manner, and impairment of endothelial dependent relaxation of the brachial artery was observed in young smokers [9]. The ACE inhibitor captopril was used to investigate whether ACE inhibition is able to protect endothelial function against deleterious effects of passive cigarette smoking. Indeed, captopril prevented the depression of acetylcholine induced relaxation of the aorta. The mechanism of this protection is not clear. Although plasma angiotensin (Ang) II rose acutely within 30 min of smoke exposure in dogs [10], the activity of ACE was found to be decreased in chronic smokers [11]. On the other hand, plasma catecholamine level was increased [12], the sympathetic nervous system was activated [2], and mean blood pressure was enhanced [3] in active smokers and in our model of passive smoking rabbits plasma norepinephrine level was increased [13]. Thus we suggest that the protective effect of captopril on endothelial function might have been caused by removal of the facilitating effect of Ang II on sympathetic drive and concomitant hypertension. This suggestion is supported by the findings of Moreau et al. [14], when AT1 receptor antagonist losartan exerted its protective effect in spontaneously hypertensive rats by a sympathoinhibitory effect, predominantly on the prejunctional level. However, the molecular basis of endothelial protection may also involve the potential antioxidant effect of the SH group in the captopril molecule [15]. Further studies are needed to provide better understanding of changes in reactivity of aorta during passive smoking.

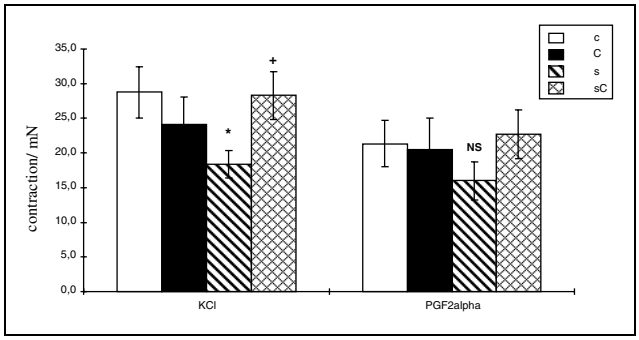

Fig. 1: Changes in the contraction of aorta to potassium chloride (KCl) and to prostaglandin (PG) F2alpha; values are means ± S.E.M.; * $P \leq 0.05$ compared to control; + $P \leq 0.05$ compared to previous group, $N = 8$ in each experimental group c – control, cC – control + captopril, s – passive smoking, sC – passive smoking + captopril

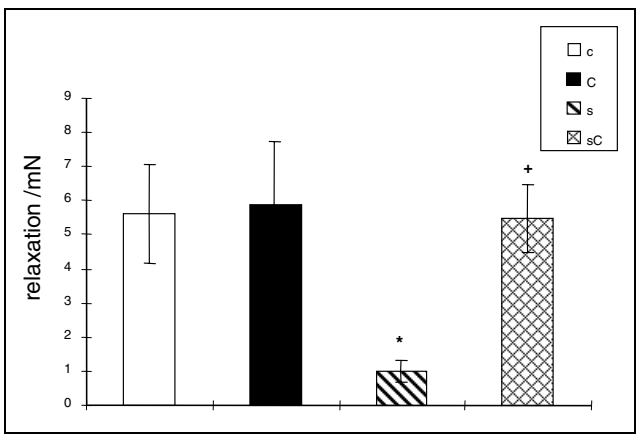

Fig. 2: Changes in the acetylcholine induced relaxation of aorta; values are means ± S.E.M.; * – $P \leq 0.05$ compared to control; + $P \leq 0.05$ compared to previous group, legend as in Fig. 1

References

1 Zhu, B. Q.; Parmley, W. W.: Am. Heart J. **130**, 270 (1995)
2 Winniford, M. D.: J. Hypert. **8** (suppl), S17 (1990)
3 Houdi, A. A.; Dowell, R. T.; Diana, J. N.: J. Pharmacol. Exp. Ther. **275**, 646 (1995)
4 Gvozdjakova, A.; Simko, F.; Kucharska, J.; Braunova, Z.; Psenek, P.; Kyselovic, J.: Biofactors **10**, 61 (1999)
5 Simko, F.; Braunova, Z.; Kucharska, J.; Bada, V.; Kyselovic, J.; Gvozdjakova, A.: Pharmazie **54**, 314 (1999)
6 Simko, F.; Pechanova, O.; Bernatova, I.; Holecyova, A.; Simko, J.; Sochorova, R.: Physiol. Res. **47**, 103 (1998)
7 Simko, F.; Martinka, P.; Brassanova, J.; Klimas, J.; Kyselovic, J.: Pharmazie **54**, 630 (1999)
8 Ota, Y.; Kugiyama, K.; Sugiyama, S.; Ohgushi, M.; Matsumura, T.; Doi, H.; Ogata, N.; Oka, H.; Yasue, H.: Atherosclerosis **131**, 195 (1997)
9 Celermajer, D. S.; Sorensen, K. E.; Georgakopoulos, D.; Bull, C.; Thomas, O.; Robinson, J.; Deanfield, J. E.: Circulation **88**, 2149 (1993)
10 Clark, W. R.; Molteni, A.; Nieman, G.; Brizio-Molteni, L.; Solliday, N. H.: Ann. Clin. Lab. Sci. **19**, 452 (1989)
11 Haboubi, N. A.; Bignell, A. H.; Haboubi, N. Y.: Clin. Chim. Acta **154**, 69 (1986)
12 Trap-Jensen, J.: Am. Heart J. **115**, (1Pt 2) 263 (1988)
13 Török, J.; Gvozdjakova, A.; Kucharska, J.; Balazoviech, I.; Kysela, S.; Simko, F.; Gvozdjak, J.: Physiol. Res. **49**, 135 (2000)
14 Moreau, N.; Richer, C.; Vincent, M. P.; Guidicelli, J. F.: J. Cardiovasc. Pharmacol. **22**, 126 (1993)
15 Bartosz, M.; Kedziora, J.; Bartosz, G.: Free Rad. Biol. Med. **23**, 729 (1997)

Received July 27, 2000
Accepted October 22, 2000

Prof. Fedor Simko, MD, PhD
Department of Pathophysiology
School of Medicine
Sasinkova 4
813 72 Bratislava
Slovak Republic
simko@med.uniba.sk