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Editorial comment to “Cytokines present in smokers’ serum interact with smoke components to enhance endothelial dysfunction” by Barbieri et al.

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Cigarette smoking (CS) is the most addictive but modifiable habit and a major health hazard. Smoking primarily affects respiratory tract and causes chronic obstructive lung diseases and cancers of the lung and pharynx. Smoking is also a major independent risk factor for atherosclerotic vascular diseases, including coronary artery disease and cerebrovascular attack. Smoking-related respiratory diseases can be explained by the direct exposure to cigarette smoke. In contrast, the mechanisms responsible for the acceleration atherosclerosis by CS are still elusive, although deleterious effects of CS on the cardiovascular system are well established.[1]

The exact toxic components of cigarette smoke are largely unknown and the mechanisms of vascular damage induced by CS are likely multifaceted. However, increasing evidence suggests that oxidative stress and inflammation, which are also closely interrelated, play critical roles in the mechanism for the pathophysiological link between CS and vascular injury leading to the development of atherosclerosis.[2]

In this issue of Cardiovascular Research, Barbieri et al reported an interesting study showing that serum from active smokers induced reactive oxygen species (ROS) production from NADPH oxidase and cyclooxygenase (COX)-2 expression through activation of p38MAPK/Akt pathway in endothelial cells.[3] The effects of serum from active smokers were blocked by simultaneous immuno-neutralization of interleukin (IL)-1β and tumor necrosis factor (TNF)-α and were mimicked by addition of tobacco smoke extract (TSE) to IL-1β and TNF-α, indicating the synergy between inflammatory cytokines derived from smokers and circulating component of cigarette smoke. The authors also showed that injection of TSE and IL-1β /TNF-α induced ROS production in the carotid artery of mice.

Cigarette smoke can be divided into two phases: a particulate (tar) phase and a gas phase. Both phases contain high concentration of ROS.[4] In addition, previous studies have shown that aqueous cigarette extracts contain pro-oxidant substances that induce ROS production in the blood vessel.[5] These soluble

substances are likely to get into the bloodstream and affect both systemic and pulmonary vascular beds. It is suggested that NADPH oxidase in the blood vessel is responsible for the production of superoxide upon exposure to TSE. Several studies have identified cigarette smoke component such as benzopyrene[6] and acrolein[7] as a ringleader of NADPH oxidase activation. However, cigarette smoke contains more than 4,000 known substances, of which only a part of these substances are examined individually. Therefore, it seems to be impossible to identify the exact substances in the TSE responsible for the synergistic activation of NADPH oxidase with inflammatory cytokines.

Barbieri et al[3] also showed that serum from active smokers and TSE+IL-1β/TNF-α induced translocation of p47phox, a subunit of NADPH oxidase, to the membrane and ROS production via NADPH oxidase in endothelial cells, which are consistent with previous reports. It is not clear, however, why the authors failed to see ROS production by TSE alone, which is reported in other studies.[5, 7] Although it is mentioned that TSE was prepared based on the Federal Trade Commission standard protocol, a small difference of TSE preparation may affect the results. Some other studies used commercially available TSE.[5] Therefore, it seems that comparison of the results between the related studies may be difficult without strict standardization of TSE.

Oxidative stress reduces bioavailability of nitric oxide (NO), resulting in the endothelial dysfunction. In addition, free radicals oxidize and deplete tetrahydroxybiopterin, a critical co-factor of endothelial NO synthase (eNOS), resulting in the eNOS uncoupling and superoxide production. ROS as well as TSE cause activation of redox-sensitive transcription factors such as nuclear factor-κB,[8] which is involved in the expression of many inflammation-related genes. Altogether, CS-induced oxidative stress is believed to induce endothelial dysfunction.[9]

In terms of the in vivo study by Barbieri et al,[3] injection of TSE and IL-1β /TNF-α to mice seems to induce ROS production not only in the endothelium but also medial layer of the carotid artery (Figure 4). This may suggest that CS also affects

medial smooth muscle cells. A recent study showed that both endothelium-dependent and endothelium-independent vasodilation were impaired in the male smokers,[10] which may be consistent with the results by Barbieri et al.[3] Unfortunately, it is not examined in the present study whether injection of TSE and IL-1β /TNF-α affects endothelium-dependent and independent vasodilation. And the effect of TSE and IL-1β /TNF-α on vascular smooth muscle cells is not known, either. These issues may be worth addressing in the future.

Cigarette smoking also causes inflammation of blood vessel. Several studies have shown that CS increases the number of peripheral blood leukocytes by about 20%[11] and serum levels of pro-inflammatory cytokines[12] such as IL-1β, IL-6, and TNF-α as reported by Barbieri et al.[3] These cytokines are supposed to derive from lung and leukocytes activated in the pulmonary circulation. The increased oxidative stress and circulating cytokines cause inflammation of blood vessel and endothelial dysfunction. Inflamed vessel expresses adhesion molecules such as ICAM-1 and VCAM-1, which recruit activated leukocytes that release pro-inflammatory cytokines to the blood vessel. ROS and inflammatory cytokines are also produced from inflamed blood vessel, indicating that these processes form a vicious circle. Given an important role of the interaction between activated leukocytes and blood vessel in endothelial dysfunction, it may be interesting to examine whether the combination treatment with TSE and IL-1β/TNF-α affects expression of adhesion molecules and adhesion of leukocytes to endothelial cells in the future.

In conclusion, Barbieri et al showed an intriguing interaction between TSE and inflammatory cytokines that causes endothelial dysfunction.[3] Investigation into the mechanisms involved in CS-related cardiovascular dysfunction is an important area of cardiovascular research and further studies are needed to elucidate the toxicity of CS. However, there is no doubt that promotion of smoking cessation is a fast and inexpensive way to reduce smoking-related diseases from a practical point of view of clinical medicine and public health.

Conflict of interest: none declared

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