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## Abstract 8

### **Tobacco Smoke Mediates a Monocytic and Endothelial Proinflammatory Activation that Synergistically Affects BBB Integrity**

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Cigarette smoke is known to contain high concentrations of free radicals and oxidants. However, virtually nothing is known about the oxidative damage associated with cigarette smoke on the human brain microvasculature and, more specifically, on the cellular components of the blood-brain barrier (BBB). In this study we assessed whether exposure to tobacco smoke (TS) affects the BBB integrity and the specific effect on BBB endothelial cells.

Our results clearly show that chronic exposure to CSSE induced the proinflammatory activation of the microvascular endothelium demonstrated by increased levels of locally secreted proinflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], and interleukin-1 beta [IL-1 $\beta$ ]). In addition, the expression level of relevant vascular adhesion molecules such as VCAM-1, P-selectin, and E-selec-

tin was also increased. Exposure to TS facilitated the differentiation of a well-known human acute monocytic leukemia cell line (THP-1) into mature and activated macrophages. This differentiation process was accompanied by a TS dose-dependent MMP-2 and MMP-9 activation. MMP activity was also detected by zymography in the culture medium of endothelial cells following the exposure to TS. These data strongly suggest that cigarette smoke synergistically modulates WBC differentiation as well as WBC and endothelial cell proinflammatory activation, thus ultimately hampering BBB integrity. BBB integrity was monitored by real-time measurements of transendothelial electrical resistance (TEER) while the levels of adenylylase kinase released in the culture medium were used to assess for cell viability.

TS exposure also caused a cellular shift toward a more anaerobic and therefore less efficient metabolism. This was determined by significant ( $P < .01$ ) increase in lactate production. Interestingly, antioxidant supplementation with vitamins C and E reduced or fully prevented the oxidation and the inflammatory damage induced by cigarette smoke.

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