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Advanced Glycated End Product Mediated Cell Activation

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Endothelin 1 (ET-1) which is released by endothelial cells is known to be one of the most potent vasoconstrictors and a mitogen to contribute to endothelial dysfunction. Patients with poor glycemic control and diabetic nephropathy have shown to have elevated levels of AGEs and elevated levels of ET-1. Therefore, we investigated whether a link exists between hyperglycemia-dependent AGE formation and induction of ET-1. We induced ET-1 by incubation of BAECs with erythrocytes isolated from diabetic patients. Erythrocytes which derived from patients with poor glycemic control had a stronger ET-1-inducing activity on BAECs than erythrocytes derived from patients with good glycemic control. Western-blot assays confirm that erythrocyte lysate from hyperglycemic patients contained more CML-modified proteins than erythrocytes from subjects with good glycemic control. Binding AGE to RAGE results in the generation of intracellular oxidative stress and activation of the redox-sensitive NF-κB. Structural analysis of the ET-1 promoter revealed a putative NF-κB binding site between -2090 and -2081 bp. Consistently, this study indicates that CML-modified proteins not only increase ET-1 concentration but also increase the expression of ET-1 mRNA in BAECs. It seems that AGE-mediated ET-1 induction in endothelial cells is at least in part dependent on an oxidant-sensitive mechanism (data not shown). In AGE/RAGE-induced cells, RAGE appears to have a central role. A successful down regulation of ET-1 mRNA synthesis could be demonstrated after incubation with sRAGE. Furthermore, AGE/RAGE mediated NF-κB activation was also dependent on RAGE, since NF-κB activity was suppressed by blocking of RAGE with excess of sRAGE or antisense RAGE oligonucleotides. Thus, AGE mediates ET-1 induction and increased expression of ET-1 mRNA is dependent on RAGE.