sion and NO release, and these effects were inhibited by SB 203580. Taken together, our data suggest that AGEs may activate cAMP-dependent protein kinase, which in turn stimulates p38 MAPK and results in iNOS induction.

Several mechanisms may be responsible for the induction of iNOS in RAW 264.7 macrophages. One of the factors is lipopolysaccharides (LPS) contaminating the BSA-AGEs preparation. Preparation of BSA-AGEs requires long-term incubation of BSA with a high concentration of glucose which may lead to bacterial contamination. Commercially available BSA may contain endotoxin which may induce iNOS expression as well. These possibilities were excluded by the facts that polymyxin B inhibited LPS-induced but not AGE-induced iNOS expression in RAW 264.7 cells.

In conclusion, this study provides evidence for a novel role of cAMP-dependent protein kinase in AGE-regulated NO production. Our results raise the possibility that diabetic complications and neurodegenerative diseases could be mediated by cAMP-induced iNOS expression.

REFERENCE

1. Amore A, Cirina P, Mitola S, Peruzzi L, Gianolio B, Rabbone I, Sacchetti C, Ceruti F, Grillo C, and Coppo R. Nonenzymatically glycated albumin (Amadori adducts) enhances nitric oxide synthase activity and gene expression in endothelial cells. *Kidney Int.* 1997;51:27-35.
2. Brett J, Schmidt AM, Yan SD, Zou YS, Weidman E, Neeper M, Przysiecki C, Shaw A, Migheli A, Stern D. Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. *Am. J. Pathol.* 1993;143:1699-712.
3. Brownlee M. Glycosylation products as toxic mediators of diabetic complications. *Annu. Rev. Med.* 1991;42: 159-66.
4. Ceriello A. Hyperglycemia: the bridge between non-enzymatic glycation and oxidative stress in the pathogenesis of diabetic complications. *Diabetes.. Nutr. Metab.* 1999;12:42-6.
5. Denhardt DT. Signal-transducing protein phosphorylation cascades mediated by Ras/Rho proteins in the mammalian cell: the potential for multiplex signaling. *Biochem. J.* 1996;318:729-47.
6. Durancy N, Munch G, Michel T, and Riederer P. Investigations on oxidative stress and therapeutical implications in dementia. *Eur. Arch. Psychiatry. Clin. Neurosci.* 1999;249:68-73.
7. Gross SS, and Wolin MS, Nitric oxide: pathophysiological mechanism. *Annu. Rev. Physiol.* 1995;57:737-69.
8. Hasegawa G, Nakano K, Sawada M, Uno K, Shibayama Y, Ienaga K and Kondo M. Possible role of tumor necrosis factor and interleukin-1 in the development of diabetic nephropathy. *Kidney. Int.* 1991;40:1007-12.
9. Higashi T, Sano H, Saishoji T, Ikeda K, Jinnouchi Y, Kanzaki T, Morisaki N, Rauvala H, Shichiri M, Horiuchi S. The receptor for advanced glycation end products mediates the chemotaxis of rabbit smooth muscle cells. *Diabetes* 1997;46:463-72.
10. Hori O, Yan SD, Ogawa S, Kuwabara K, Matsumoto M, Stern D, and Schmidt AM. The receptor for advanced glycation end-products has a central role in mediating the effects of advanced glycation end-products on the development of vascular disease in diabetes mellitus. *Nephrol. Dial. Transplant.* 1996;11:13-6.
11. Huttunen HJ, Fages C, and Rauvala H. Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF-kappaB require the cytoplasmic domain of the receptor but different downstream signaling pathways. *J. Biol. Chem.* 1999; 274:19919-24.
12. Ido Y, Kilo C, Williamson JR. Interactions between the sorbitol pathway, non-enzymatic glycation, and diabetic vascular dysfunction. *Nephrol. Dial. Transplant.* 1996; 11:72-5.
13. Khechai F, OllivierV, Bridey F, Amar M, Hakim J, and de Prost D. Role of oxidant stress and protein tyrosine kinase activation. *Arterioscler. Thromb. Vasc. Biol.* 1997; 17:2885-90.
14. Knowles RG, and Moncada S. Nitric oxide synthase in mammals. *Biochem. J.* 1994;298:249-58.
15. Lander HM, Tauras JM, Ogiste JS, Hori O, Moss RA, and Schmidt AM. Activation of the receptor for advanced glycation end products triggers a p21(ras)-de-