Syndromes of type 2 diabetes and insulin resistance are accompanied by varying degrees of hyperinsulinemia. To date, a number of epidemiological studies have suggested that elevated levels of circulating insulin contribute independently to cardiovascular risk.\(^1\,^2\) It is not surprising, however, that some studies demonstrated no, or marginally increased, risk for cardiovascular complications,\(^3\,^4\) as it is clear that insulin is not the sole culprit. Other factors, such as hyperlipidemia and even intermittently elevated levels of blood glucose, are tightly linked to syndromes characterized by elevated levels of insulin. The key, therefore, to pinpointing the potentially adverse effects of insulin on the vessel wall concerns analysis of its effects on specific properties of vascular cells.

In this issue of Circulation Research, Golovchenko et al\(^5\) have focused on the role of insulin in activation of the pleiotropic transcription factor nuclear factor-\(\kappa\)B (NF-\(\kappa\)B). This is a logical target, as evidence mounts to support a role for activation of NF-\(\kappa\)B in the pathogenesis of atherosclerosis,\(^6\,^7\) ischemia-reperfusion injury,\(^8\,^9\) and diabetes.\(^10\,^11\) For example, target genes of NF-\(\kappa\)B, such as tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and vascular cell adhesion molecule-1, have long been speculated to participate in the earliest stages of atherogenesis. Indeed, RelA/p65, one of the components of NF-\(\kappa\)B, has been identified within the nuclei of vascular smooth muscle cells (VSMCs) and mononuclear phagocytes in human atheroma.\(^12\) The key question arises, therefore, what are the molecular triggers that switch on NF-\(\kappa\)B in the vessel wall?

**Activation of NF-\(\kappa\)B: Role of AGEs**

In this context, a mixed bag of vascular-perturbing factors associated with diabetes and insulin resistance has already been linked to activation of NF-\(\kappa\)B. For example, one consequence of hyperglycemia is the generation of advanced glycation end products (AGEs).\(^13\) Interaction of these products of nonenzymatic glycation/oxidation of proteins, with their key signal transduction receptor RAGE (receptor for AGE), results in activation of NF-\(\kappa\)B in endothelial cells, mononuclear phagocytes, and VSMCs, by processes that involve, at least in part, generation of reactive oxygen intermediates and activation of p21\(^{\text{WAF}}\) and ERK1/2 kinases.\(^10\,^14\) Recently, a specific AGE, carboxy(methyl lysine) adducts of proteins, has been shown to bind RAGE and mediate cellular activation, both in vitro and in vivo.\(^15\) Evidence definitively linking RAGE to these ligand-mediated effects was demonstrated by blockade of AGE-mediated activation of NF-\(\kappa\)B in the presence of blocking antibodies to RAGE, soluble RAGE (sRAGE; the extracellular ligand-binding domain), or transient transfection into wild-type RAGE-bearing cells of a construct in which solely the cytosolic domain of the receptor was deleted. In the latter case, a dominant-negative effect resulted, as AGE-stimulated activation of NF-\(\kappa\)B was significantly suppressed.\(^15\,^16\)

**Activation of NF-\(\kappa\)B: Role of Hyperglycemia**

Indeed, hyperglycemia itself has been linked to activation of NF-\(\kappa\)B in vascular cells. Work from Nishikawa et al\(^17\) showed that exposure of cultured bovine aortic endothelial cells to physiologically relevant concentrations of glucose, 30 mmol/L, resulted in enhanced nuclear translocation of NF-\(\kappa\)B. A critical role for generation of intracellular oxidant stress, largely by mitochondrial oxidants, in glucose-mediated activation of NF-\(\kappa\)B was shown. In addition, previous studies by Yerneni et al\(^18\) indicated that exposure of VSMCs to hyperglycemia also prompted activation of NF-\(\kappa\)B. Consistent with the concept that the vascular milieu in syndromes such as insulin resistance is quite complex, those investigators found that exposure of VSMCs to TNF-\(\alpha\), platelet-derived growth factor, epidermal growth factor, or insulin-like growth factor-1 augmented the effects of hyperglycemia on NF-\(\kappa\)B activation. Together with other known stimuli linked to activation of NF-\(\kappa\)B, such as oxidized lipoproteins and angiotensin-II, it is reasonable to propose that multiple intertwined factors associated with syndromes of type 2 diabetes and insulin resistance may contribute to the process of vascular activation and atherogenesis.

**Effects of Insulin: A Priming Step in Activation of NF-\(\kappa\)B in VSMCs**

In this context, the studies presented by Golovchenko et al\(^5\) have sought to test the hypothesis that insulin alone, or in concert with other vascular-perturbing factors, modulates activation of NF-\(\kappa\)B in the vessel wall. In this study, the authors extend their previous observation that a novel property of insulin is its ability to activate prenyl transferases, farnesyltransferases, and geranylgeranyltransferases I and II.\(^19\,^20\) Because these molecules possess the capacity to posttranslationally modify Ras, Rho, and Rab proteins, their activation links them to signal transduction pathways. Golovchenko et al\(^5\) show that incubation of VSMCs with

---

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association. From the College of Physicians & Surgeons, Columbia University, New York, NY. Correspondence to Dr Ann Marie Schmidt, College of Physicians & Surgeons, Columbia University, 630 W 168th St, P&S 17-501, New York, NY 10032. E-mail ams11@columbia.edu (Circ Res. 2000;87:722-724.) © 2000 American Heart Association, Inc. Circulation Research is available at http://www.circresaha.org

---
insulin (largely at physiologically relevant doses) increased availability of geranylgeranylated Rho-A, thereby invoking an established mechanism to link increased levels of insulin to activation of NF-κB.²¹ It is important to note that insulin alone did not enhance activation of NF-κB in this system. However, in VSMCs, insulin, and AGEs, hyperglycemia or angiotensin II synergized to enhance NF-κB activation to even greater degrees than that observed by any of these mediators alone. These studies suggest that insulin primes the vasculature for enhanced activation on contact with these traditional mediators and provide support for the concept that the vascular microenvironment in type 2 diabetes or syndromes of insulin resistance is enriched in factors that appear to lead to a common pathway, activation of NF-κB.

However, these findings must be viewed in context, considering that activation of NF-κB is likely not the whole story. It is certain that other transcription factors linked to cellular stress response mechanisms act in concert with NF-κB to regulate specific gene expression. Such regulation provides an exquisite degree of specificity, for example, in individual cell types or during discrete periods of development. Therefore, future studies in this area should determine to what degree other key stress response transcription factors, such as activator protein-1,²² participate in insulin-mediated effects on vascular function.

**Is NF-κB a Logical Target for Intervention in Diabetes and Hyperinsulinemia: “Good” and “Bad” NF-κB?**

From these considerations, one might conclude that NF-κB is a logical target to prevent or suppress the vascular-perturbing properties of a range of injurious molecules linked to diabetes and insulin resistance, from oxidized lipoproteins, to AGEs, to high levels of glucose or insulin. Although results of future studies must be the final arbiter of this issue, it is highly likely that the “good” side of NF-κB will preclude its inhibition, at least in a global manner. In addition to its likely role in innate cellular defenses, the classic example of a devastating outcome secondary to lack of functional NF-κB complex was demonstrated by studies in which the RelA subunit (p65) was genetically deleted in mice. Embryonic lethality ensued, attributable to massive apoptosis of liver cells.²³ This critical finding highlighted important antiapoptotic functions (at least in certain circumstances) of NF-κB. Studies in mature animals, for example, have shown NF-κB, and one of its target genes, TNF-α, to be critical for hepatocyte recovery and regeneration after extensive hepatectomy.²⁴ The beneficial effects of enhanced activation of NF-κB are not limited to liver development or the response of this organ to extensive resection. For example, activation of NF-κB has been linked to protection against apoptosis in VSMCs²⁵ and to activation of manganese superoxide dismutase in hippocampal neurons exposed to oxidative insults.²⁶ These seeming paradoxes underscore the concept that NF-κB subserves innate functions of host defense and response, at least to certain cellular stresses.

It is important to note, however, only upon delineation of the precise molecular participants in the NF-κB cascade that mediate selectively “good” inflammation/resolution and re-

NF-κB is a pleiotropic transcription factor; friend and foe. In the context of type 2 diabetes/hyperinsulinemia, a range of environmental stimuli, such as AGEs, hyperglycemia, and angiotensin II triggers signal transduction pathways leading to NF-κB activation. Prominently included among these signaling mechanisms is a role for Ras, Rho-A, cdc42, and Rac1. The pathways detailed in the figure include multiple overlapping processes, and effector mechanisms are triggered at the level of NF-κB, an important watershed, as well as by other transcription factors and, in certain instances, by direct action of kinases. Nuclear translocation of NF-κB leads to activation of a range of genes involved in host and cellular defense responses. In certain settings, activation of NF-κB may lead to “good” inflammation, manifested by resolution and regeneration, or “bad” inflammation, causing tissue destruction. However, it is likely that separation of good from bad inflammation triggered by NF-κB will be difficult because mechanisms underlying both operate in tandem, delicately balanced, under many conditions. These considerations highlight possible complexities resulting from inhibition of NF-κB activation. Thus, blockade of the interaction of the cellular surface with key elements of the diabetic microenvironment, as above, may hold the key to ensuring limited inflammatory responses that restore homeostasis.

generation versus “bad” inflammation/tissue injury and loss, may blockade of NF-κB be a tenable target for therapeutic intervention (Figure). It is possible, however, that both the exquisite regulation of activation of NF-κB,²⁷ as well as the extensive network of crosstalk among the pathways, will reduce the feasibility of targeting NF-κB. In the end, it is likely that blockade of triggering events at the cell surface will provide the most logical site to dissect beneficial, innate host responses, from those that otherwise lead to a smoldering cascade of ongoing cellular activation and irreparable damage. Furthermore, identification of the full range of genes turned on by mediators in type 2 diabetes/hyperinsulinemia, such as insulin, AGEs, hyperglycemia, and oxidized lipoproteins, will shed light on multiple and, possibly, unique sites.
for intervention. The emerging use of microarray technology, indeed, represents a most potent tool in the vascular biology of diabetes and insulin resistance.

References


Key Words: insulin ■ oxidant stress ■ Rho GTPases ■ nuclear factor-κB

Downloaded from http://circres.ahajournals.org/ by guest on November 1, 2017
Hyperinsulinemia and Vascular Dysfunction: The Role of Nuclear Factor-κB, Yet Again
Ann Marie Schmidt and David M. Stern

Circ Res. 2000;87:722-724
doi: 10.1161/01.RES.87.9.722

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/87/9/722

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/