Metalloproteinases Damage the Insulin Receptor to Cause Insulin Resistance in Spontaneously Hypertensive Rats

H. Glenn Bohlen

The elegant study by Delano and Schmid-Schönbein1 points to a potentially very important overlap of an insulin resistance mechanism with hypertension in the spontaneously hypertensive rat (SHR). Their investigation will likely be important to both the obese and hypertensive populations. With the national and international emphasis on obesity and its attendant cardiovascular problems, there is a tendency to forget that essential hypertension affects about the same percentage of humans as does serious obesity and an even higher percentage of the population than does type 2 diabetes mellitus. Obesity leading to insulin resistance and, in severe situations, type 2 diabetes mellitus, does have a genetic predisposition that the patient’s lifestyle can mitigate. However, hypertension even in the lean population has an established genetic basis and often develops despite every attempt to avoid inappropriate lifestyle issues. There is obviously an overlap of the obese and hypertensive genetic populations and likely a sharing of some mechanisms to cause many of their common vascular and cardiac pathologies.

The existence of insulin resistance in the SHR came to attention in 1988 by a study by Horl et al.2 At the time, this seemed rather unusual, because the SHR is generally quite lean, and the dependence of insulin resistance on some degree of obesity was a common concept. In 1991, Reaven and Chang3 and Reaven4 questioned whether the insulin resistance leads to hypertension or vice versa in the SHR and hypertensive humans. The interest in hypertension and insulin resistance since 1988 has generated >200 articles dealing with various issues of insulin resistance in the SHR with something of the order of 5000 articles on insulin resistance and blood pressure abnormalities in humans and animals. We in clinical and basic sciences have been so well informed on this issue that we collectively take insulin resistance and some degree of hypertension as an expected relationship. What we often question is which of these abnormalities occurs first. This question is partially addressed in the study by Delano and Schmid-Schönbein1 in the context that elevated arterial pressure may be the first step in the activation of matrix-degrading metalloproteinases (matrix metalloproteinase [MMP]-9) that appears to be quite important in the cascade to insulin resistance. The Figure presents a hypothetical scheme of hypertension leading to an inflammatory state associated with increased oxygen radical generation and metalloprotease release. The assumption of hypertension leading to this status is highlighted as a question mark, because the links in this process are both complicated and, likely, interactive.5 For example, the source of oxygen radicals in hypertension may start with increased NADPH oxidase activity but progress to uncoupling of endothelial NO synthase as endothelial cells are compromised.6 In either or both scenarios, oxygen radicals can act as vasoconstrictors for vascular muscle and injury agents for endothelial cells to limit NO and other endothelial-dependent vasodilators. However, it now appears that oxygen radical issues are only part of the scheme leading to elevated vascular resistance. It is particularly important to learn from the study by Delano and Schmid-Schönbein1 that part of the inflammatory process is cell surface receptor damage by MMP-9. Although the emphasis of the study is the insulin receptor, it is reasonable to suspect that many cell surface proteins could be vulnerable to damage and, consequently, disturbing regulation of endothelial and vascular muscle cell functions. This may lead to an understanding as to why there are so many different abnormalities associated with hypertension. For example, in the hypothetical scheme of the Figure, a potential problem is the mild hyperglycemia secondary to insulin resistance associated with MMP-9 damage. In insulin-resistant rats, endothelial generation of NO is much more easily compromised by mild hyperglycemia through a protein kinase C mechanism than what occurs in lean animals.7 Even if future studies only support the clear linkage of hypertension to insulin receptor cleavage in the current study of SHRs, this observation should lead to many studies of how these 2 problems perhaps interact. To what extent this interaction is part of the cause or consequences of mechanisms associated with hypertension will remain controversial for some time to come. However, it is tempting to speculate that treatment of hypertension may be inadvertently improving insulin sensitivity and likely many other abnormalities associated with cell surface receptors that have been unknowingly damaged by protease activation associated with elevated blood pressure.

The analysis by Delano and Schmid-Schönbein1 that there is an abnormality of protein proteolysis damaging cell surface receptors during hypertension actually developed from their previous studies of cardiovascular shock. Inadequate intestinal blood flow has a deleterious component caused by proteolytic digestive enzymes, most of which are of pancreatic origin in the intestinal chyme.8,9 Their model of shock induced after reperfusion injury of the intestinal vasculature was associated with factors in
plasma that activate neutrophils and lead to increased neutrophil-endothelial cell interaction as evaluated in skeletal muscle venules and death of parenchymal cells. These abnormalities were largely avoided by treatment with an intraintestinal pancreatic protease inhibitor. Their extension of these observations in a model of shock to potential problems in hypertension was a unique insight, although completely different proteases are involved. What is particularly important is that their current data indicate that, in the SHR, suppression of matrix-degrading metalloproteinases (MMP-9) improves insulin resistance by protection of the insulin receptor from autodigestion and lowered elevated hemoglobin glycation plus lowered arterial pressure and evidence of oxidant stress. By using the in vivo microvascular endothelium as their target organ for analysis, their data are highly relevant to the vascular tissues that primarily increase vascular resistance and, in doing so, support hypertension. In the hypothetical scheme shown in the Figure, the cascade of events all lead to a positive feedback to increase resistance and thereby blood pressure to enforce the abnormality. The study by Delano and Schmid-Schöenbein\(^1\) clearly demonstrates that just limiting the actions of MMP-9 was enough to lower the hypertension in SHRs to remarkably close to normal. It is tempting from the hypothetical model to credit their finding of less insulin resistance with MMP-9 suppression as a major step in ultimately lowering vascular resistance. However, many other mechanisms are likely improved. For example, in earlier studies, the Schmid-Schöenbein group\(^{10,11}\) has shown leukocyte biology changes in SHRs in blood counts and reactivity increase. This indicates a generalized inflammatory state that is convincingly suppressed in the current study by MMP-9 inhibition. Additional systemic data are the decline in both plasma glucose and hemoglobin glycation in SHRs with treatment. Although neither plasma glucose nor hemoglobin glycation is particularly abnormal in SHRs compared to what would be found in obese rat models, they are elevated appreciably above the values in Wistar-Kyoto rats and lowered by MMP-9 suppression. The elevated glycation of hemoglobin in SHRs is particularly interesting, because there must be times when the blood glucose is substantially elevated, such as during postprandial feeding, and the glycation reflects abnormalities in glucose metabolism secondary to suppressed insulin receptor function. These observations can only mean that the consequences of hypertension potentially through the increased proteolytic activity have effects for every cell of the body, and, as such, hypertension is not just a cardiovascular system disease.

As a final note, the commentary on this study is recognition of more than just 1 study. Drs Delano and Schmid-Schöenbein and their many colleagues have been championing the problems of oxidant stress and its consequences and mechanisms in hypertension for many years. Many of the molecular localization techniques so vital to the current study were developed or refined by this group over more than a decade of work. As mentioned earlier, the current study\(^1\) of proteolytic damage during hypertension developed in part from their elegant studies of microvascular damage and neutrophil activation subsequent to pancreatic proteases during hypotension. The current study and those previously on shock undoubtedly will raise many issues of just how extensive autodigestion secondary to intestinal-pancreatic protease and matrix-degrading metalloproteinase issues may pertain to many vascular and parenchymal diseases. However, their studies are opening a new avenue for exploring the generalized consequences of hypertension and other deleterious vascular mechanisms that appear to have far more complex abnormalities than just those involving the microvasculature.

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**Disclosures**

None.
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