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Forum Review

Adverse Effects of Reactive Oxygen Species on Vascular Reactivity in Insulin Resistance

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ABSTRACT

Insulin resistance (IR) has adverse effects on the reactivity of arteries and arterioles and promotes arterial hypertension and vascular occlusive diseases. Altered reactivity of resistance vessels occurs at both the endothelium and smooth-muscle levels. One major mechanism of vascular dysfunction with IR involves the augmented generation, availability, and/or actions of reactive oxygen species (ROS). Scavengers of ROS are able immediately to restore normal dilator responsiveness in arteries from IR animals. Other factors, such as increased importance of constrictor agents such as endothelin, also restrict normal dilator responses. The basis of ROS-mediated vascular dysfunction in IR may be secondary to underlying inflammatory processes throughout the arterial wall. Although ROS scavengers may be beneficial in the short term, prolonged treatments involving behavioral approaches, such as changes in diet, weight loss, and regular exercise, and pharmacological approaches, involving the use of insulin-sensitizing agents, inhibitors of the renin–angiotensin system, or administration of statins, appear to offer benefits against the detrimental vascular effects of IR. Nonetheless, the most effective approach appears to involve prevention of IR via adoption of a healthy lifestyle by young people. *Antioxid. Redox Signal.* 8, 1131–1140.

INTRODUCTION

INSULIN RESISTANCE (IR) is a major and growing health care problem throughout the world and is a key component of the metabolic syndrome, which represents a major risk factor for the development of cardiovascular disease (1, 14, 19, 21, 30, 33, 37, 38, 42, 46, 92, 104). The reduced ability of insulin to stimulate glucose uptake into skeletal muscle (21) results in glucose intolerance, which is compensated for by prolonged hyperinsulinemia. Eventually, pancreatic β-cells fail to secrete sufficient insulin, leading to non–insulin-dependent diabetes mellitus (NIDDM; type II diabetes). The exact mechanism for the development of IR remains unclear, but current evidence indicates the sequential involvement of obesity-associated visceral adiposity, increased secretion and peripheral actions of adipocytokines, and impairment of insulin-receptor function and/or insulin receptor/intracellular signal coupling (20, 21, 38, 42, 45, 53, 68, 105). Insulin resistance also is present with many other clinical conditions, such as polycystic ovary syndrome, trauma, and premature birth (10, 11, 18, 56, 64, 65, 79).

The purpose of this review is to summarize our current understanding of the impact of IR on arterial reactivity and to indicate possible underlying mechanisms such as augmented levels of reactive oxygen species (ROS) involved in vascular dysfunction. Although ROS are normal regulators of vascular tone (40), excessive levels of ROS during pathologic conditions appear to lead to inappropriate alterations in reactivity (40, 49). We include information from a variety of arteries to illustrate the diversity of regional circulatory responses that occur in IR. The results discussed are derived largely from studies on rodent models of IR, but experimental data derived from human studies as well as from those of other species are becoming increasingly available and also are discussed.

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USEFULNESS OF ANIMAL MODELS OF IR

Examination of the vascular effects of insulin resistance in people is complicated by the presence of other clinical conditions and various medications that affect reactivity. We have found two rat models of IR, the Zucker (fa/fa) obese rat (studied at 12 weeks) and the fructose-fed rat (studied at 10 weeks), particularly useful in our experiments, because we can largely separate the IR syndrome from confounding factors such as hypertension and hyperglycemia. The etiology of IR in the Zucker obese rat is due to a defect in the gene for the leptin receptor (116), whereas a nutritional change leads to IR in the Sprague–Dawley rats on a high-fructose diet (53, 73). During the initial phase of IR, these two types of animals demonstrate severe hyperinsulinemia but have normal fasting blood glucose levels and are not hypertensive (24–26). Fructose-fed rats have normal total cholesterol levels, low high-density lipoprotein levels, and elevated triglyceride levels compared with Sprague–Dawley rats on a normal diet (54, 78). Compared with fructose-fed and normal rats, Zucker obese rats have elevated blood total cholesterol levels and a 3- to 5-times greater elevation of triglyceride levels (32), and therefore the Zucker obese rats can be thought of as having a more advanced or at least a more complicated form of IR. At a later stage of IR in both rat models, vascular dysfunction becomes more severe, and the rats become hypertensive (53). The Zucker obese rats that we use are different from the Zucker diabetic fatty (ZDF) rats, a model of early-onset type II diabetes (119). In addition to the two rat models of IR that we use, other animal models using other strains of rats, mice, pigs, and various other species have been studied and have provided useful information on cardiovascular consequences of IR (85, 117). Although it is more difficult to acquire data on vascular effects of IR from people because of obvious technical and subject-related limitations, it is remarkable how closely the findings from humans parallel those derived from experimental animals.

IMPAIRMENT OF ENDOTHELIUM-DEPENDENT DILATOR RESPONSES

Endothelium produces several important vasodilator substances (32), including prostaglandins, nitric oxide (NO), and endothelium-derived hyperpolarizing factor (EDHF). These substances can diffuse to vascular smooth muscle (VSM), where they activate receptors or second-messenger systems or both, or directly hyperpolarize VSM via gap junctions between endothelium and VSM (32). The relative importance of any one of these endothelium-derived relaxing agents depends on species, age, regional circulation, gender, and vascular segment studied. A consistent finding is that IR reduces the dilator ability of one or more of the endothelium-dependent dilator agents in virtually all of the circulations examined (17, 22, 26, 27, 35, 47, 49, 52, 75, 86, 109). Similar findings concerning impairment of endothelium-dependent dilation in IR people have been derived from several regional circulations (3, 6, 9, 11, 13, 43). Conversely, endothelium-dependent dilator responses can remain intact in arteries from IR animals (51), and normal responsiveness involving one endothelium-derived relaxing factor may coexist with diminished responsiveness to another factor (86). We are unaware of situations in which dilator responses to any endothelium-derived relaxing factor are enhanced in IR.

Several factors may lead to reduced endothelium-dependent dilator responsiveness. These include the (a) attenuated production of the dilator substance by endothelium (49, 99–101); (b) augmented degradation of endothelium-derived dilator substances before activating signaling pathways in VSM (26); (c) impaired intracellular signaling in VSM (17, 27, 94, 97, 110, 116); and (d) enhanced production or potency of opposing, endothelium-derived, or neurally-derived constrictor agents (34, 50, 77). Our laboratory has provided examples for each of these situations. First, in the mesenteric arteries of fructose-fed rats, the EDHF component of the dilator responses to bradykinin and acetylcholine is diminished because of a reduction in cytochrome P-450 activity (49). However, the NO-dependent portion to the arterial response to these agents was intact (75). Second, NO-dependent dilation in the basilar artery of Zucker obese rats is impaired because of augmented degradation of NO before it can affect tone of VSM (27) (Fig. 1). The reduced NO-dependent dilator response in the basilar artery is even more striking because levels of endothelial nitric oxide synthase (eNOS) in cerebral arteries are increased in Zucker obese rats (27). Similarly, in coronary arteries of Zucker obese rats, NO-mediated dilation to insulin is reduced in IR despite an increase in eNOS levels (51). Third, prostaglandin-dependent dilation in the middle cerebral artery of fructose-fed rats is reduced because of the impairment of calcium-activated potassium (K_{Ca}) channels coupled to prostaglandin receptors in VSM (25, 26). And fourth, insulin-dependent dilator responses in the mesenteric arteries of fructose-fed rats are reduced in part by enhanced constrictor effects of endothelium-derived endothelin on VSM (77). Enhanced endothelin activity associated with increased receptor expression was observed in mesenteric arteries of fructose-fed rats (50).

IMPAIRMENT OF POTASSIUM CHANNEL FUNCTION IN VSM

The potassium channels involved in mediating responsiveness of arteries and arterioles to various physiologic stimuli arising from the endothelium, blood, perivascular nerves, or parenchyma are the adenosine triphosphate (ATP)-sensitive (K_{ATP}), K_{Ca}, inwardly rectifying (K_{ir}), and voltage-sensitive (K_v) potassium channels (32). Activation of VSM potassium channels with resultant hyperpolarization directly promotes dilation, as in the case of K_{ATP} channels (99), or can act to "buffer" or limit responses to vasoconstrictor stimuli, as occurs with K_{Ca} channels. Additionally, K_{Ca} and K_v channels are tonically active in the cerebral circulation, and inhibition of these channels constrict the cerebral arteries (25–27).

Several studies in experimental animals have shown that VSM potassium channel function is impaired in IR. We are unaware of any studies addressing this issue in people with IR. In the original series of studies in this area, Miller and

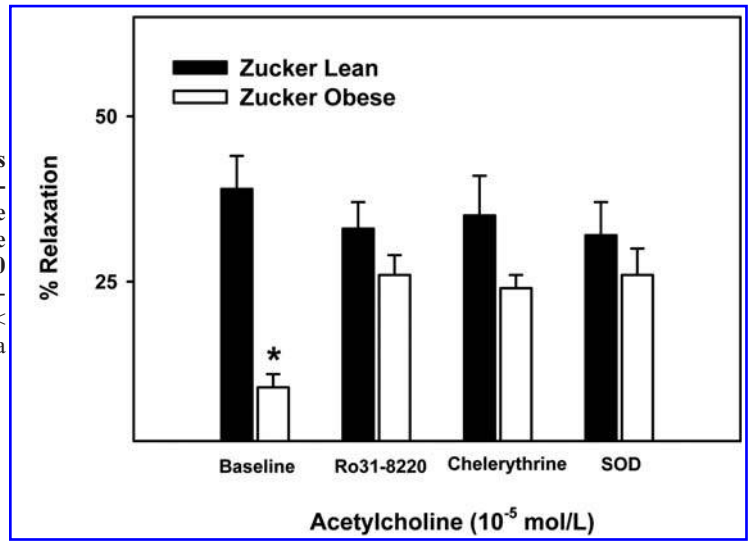

FIG. 1. Restoration of normal dilator responses of side branches of the basilar artery to acetylcholine in the Zucker obese rat by protein kinase C inhibitors [Ro31–8220 (5 *M*)] or chelerythrine (1 μ*M*)] or superoxide dismutase (SOD; 150 units/ml). Acetylcholine is an endothelium-dependent dilator agent in the basilar artery of the rat. *$p <$ 0.05, compared with response in ZL artery. Data from ref. 27.

colleagues demonstrated that K_{Ca} channel function is impaired in mesenteric arteries of IR rats (17, 49, 52, 73, 74, 76). Impaired K_{Ca} channel function was verified by both *in vitro* diameter and patch-clamp approaches. Conversely, K_{ATP}-mediated dilator responses are intact in this circulation despite IR.

Recently, we showed that both K_{ATP} and K_{Ca} channels are impaired in middle cerebral arteries of fructose-fed IR rats, whereas the K_v and K_{ir} channels are functionally intact (26). Additionally, all four types of potassium channels listed earlier are impaired in the more severely affected Zucker obese rats (27) (Fig. 2). Similar findings were reported recently by another laboratory (86). Impaired potassium channel function is not due to reduced density of K^+ channels in these arteries. By using immunoblot analysis, we found that levels of the $BK_{Ca\alpha}$, K_{ir} 6.1–6.2, and K_{ir} 2.1 proteins (the pore-forming subunits of the BK_{Ca}, K_{ATP}, and K_{ir} channels, respectively) are not detectably affected by IR in either the fructose-fed (26) or Zucker obese (27) rats. These findings are consistent with the results of a previous study in which the expression of the $BK_{Ca\alpha}$ subunit in mesenteric arteries was found to be unaffected by IR (17).

MECHANISMS OF IMPAIRMENT OF VASCULAR FUNCTION IN IR

The underlying causes of vascular dysfunction in IR are incompletely understood, but we and others have suggested a critical role of ROS resulting from IR-induced vascular inflammation or from other IR-related effects (17, 26, 27, 86, 97) (Figs. 3 and 4). Vascular inflammation, characterized by an elevation in levels of C-reactive protein, interleukin-6, tumor necrosis factor-α, platelet-activating factor, and fibrinogen (1, 12, 19, 42, 91) is associated with elevated ROS levels in arteries from several animal species including humans (27, 41, 48, 99, 101, 115). Augmented vascular ROS levels have been shown to affect en-

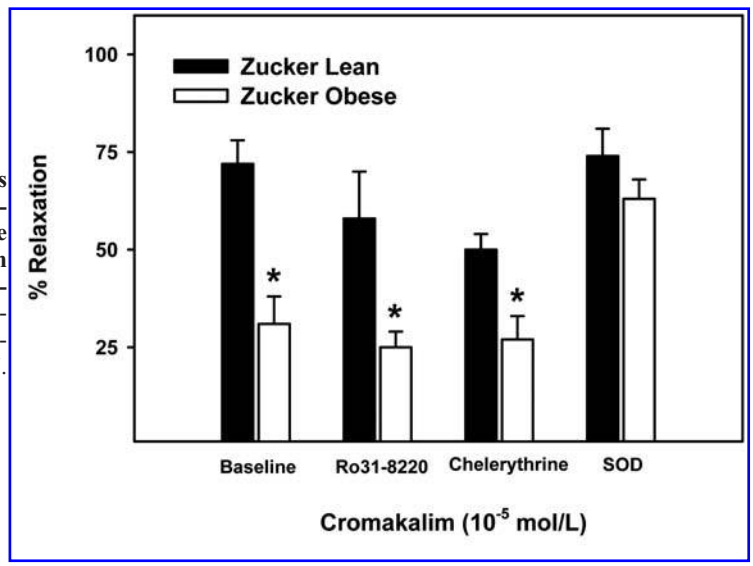

FIG. 2. Restoration of normal dilator responses of side branches of the basilar artery to chromakalim in the Zucker obese rat by superoxide dismutase (SOD; 150 units/ml) but not by protein kinase C inhibitors [Ro31–8220 (5 μ*M*)] or chelerythrine (1μ*M*)]. Chromakalim dilates VSM directly by activation of K_{ATP} channels. *$p < 0.05$, compared with response in ZL artery. Data from ref. 27.

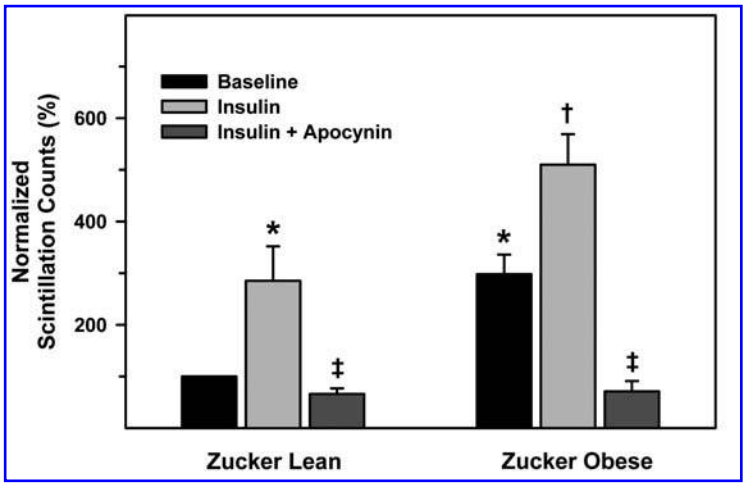

FIG. 3. ROS production in coronary arteries from ZO and ZL rats is higher under baseline conditions and during insulin application (330 ng/ml) and is substantially attenuated by a NAD(P)H oxidase inhibitor (apocynin; 10 μ*M*). ROS production for the coronary arteries was measured by using the lucigenin-enhanced chemiluminescence method. *$p <$ 0.05, compared with ZL baseline. †$p < 0.05$, compared with ZL insulin treatment. ‡$p < 0.05$, compared with insulin treatment without apocynin. Data from ref. 51.

dothelium- and potassium channel–dependent dilator responses in a variety of settings including IR (2, 4, 26, 27, 62).

ROS could affect vascular reactivity via direct actions on ion channels, receptors, and signaling pathways, or their effects could involve additional steps involving protein kinases and subsequent changes in receptor function or activity of signaling pathways (8, 106). For example, we have shown that ischemia/reperfusion in the cerebral circulation transiently inhibits arterial K_{ATP} function via a ROS-dependent mechanism (4). ROS also are able to degrade NO and thus reduce dilator responses (27), and elevated ROS levels in endothelium may affect levels of enzymes involved in production of dilator agents or inhibit activity of these enzymes (20, 32). Furthermore, impairment of endothelium-dependent dilation in cerebral arteries of Zucker obese rats is reversed by both ROS scavengers and protein kinase C (PKC) inhibitors, thereby suggesting an interaction between ROS and PKC-derived phosphorylation events in promotion of vascular dysfunction

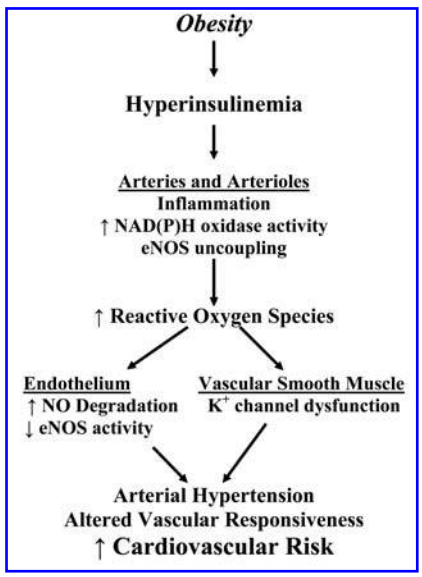

FIG. 4. Schematic depiction of major elements involved in the perturbation of vascular dysfunction in insulin resistance.

(27) (Figs. 1 and 2). The species of oxygen radicals responsible for IR-mediated dysfunction of cerebral vascular potassium channels and endothelium-dependent response is not known with certainty but, based on recent data from our laboratory, it may be superoxide anion or a superoxide anion–derived radical (26, 27). Nonetheless, identification of the species of oxygen radicals involved is an area deserving further investigation.

Elevated ROS levels are present in various arteries from IR rats in endothelium, VSM, and adventitia (26, 27, 51), which is consistent with the general vascular dysfunction seen in this disease (8, 12, 39, 48, 56, 67, 91, 114) (Fig. 3). A striking finding from our recent studies is that despite established IR in two rat models, application of superoxide dismutase alone or together with catalase leads to immediate restoration of normal responsiveness to endothelium- and potassium channel–dependent dilator stimuli (26, 27) (Figs. 1 and 2). The finding that ROS are able to exert continued inhibitory effects on potassium channel function without causing permanent changes in channel characteristics is supported by patch-clamp studies performed in myocytes from mesenteric arteries of fructose-fed rats (17). Thus, agonist-induced BK_{Ca}-channel activity was impaired when examined in a cell-attached configuration but was normal when the membrane patch was separated from the cell in an inside-out configuration. This finding indicates the presence of endogenous inhibitory substances such as ROS that are able to affect vascular reactivity without permanently changing potassium channel characteristics. However, the duration of IR present in rats and other species is only a matter of a few weeks or several months, and it is unclear whether vascular dysfunction in IR of more prolonged duration, such as decades, as seen in people, would be so readily reversed with ROS scavengers.

Although the underlying etiology and metabolic derangements are different between type I diabetes and IR, subsequent mechanisms of vascular dysfunction appear to be similar for these two diseases. Thus, enhanced ROS levels during type I diabetes also appear to account for reduced endothelium- and VSM potassium channel–dependent dilations in a wide variety of regional circulations from experimental animals and people (31, 40, 119). For example, hyperglycemia-induced production of excessive amounts of superoxide anion enhances degradation of NO (69) and reduces K_v channel

opening (63) and K_{ATP} channel function (80) in rat coronary arteries. Additionally, K_{ir} and K_{Ca} channels are impaired in cerebral arteries of diabetic rats (70). Conversely, mechanisms involving hydrogen peroxide but not superoxide anion appear to mediate K_{Ca} channel impairment in type I diabetes (108). Although not so well studied as IR or type I diabetes, ROS also appear to be the mediators of vascular dysfunction in type II diabetes (16, 83, 95).

The augmented ROS production in IR may involve several distinct pathways (2, 7, 41, 59, 81). Recent findings indicate that nicotinamide adenine dinucleotide phosphate, [NAD(P)H]-oxidase activity, an important source of vascular superoxide anion, is augmented in cerebral and coronary arteries from IR rats (26, 27, 107) (Fig. 3). Another source of superoxide anion in IR may arise from the imbalance in levels of eNOS and its essential cofactor, (6*R*)-5,6,7,8-tetrahydrobiopterin (BH_4). Although eNOS has been shown to be elevated in cerebral and coronary arteries from IR animals (27, 55, 57), perhaps in compensation for reduced NO bioavailability, BH_4 levels are suboptimal, possibly leading to enhanced superoxide anion formation at the expense of NO production because of uncoupling of NOS (41, 99–101). Dietary supplementation of BH_4 leads to decreased oxidative stress and restoration of endothelial function, through increased NO production or NO stability (100). Additional pathways leading to increased ROS production during IR may involve metabolism of arachidonic acid via several enzymatic pathways (2), metabolism of xanthine by xanthine oxidase system (32), or enhanced production of superoxide anion from mitochondria (36).

Whereas ROS appear to be a major cause of reduced dilator responses in IR, other mechanisms such as enhanced constrictor effects via increased sympathetic nervous system activity (34) or augmented release of endothelin (77) also may be involved in some situations. It is unclear whether an increased contribution to vascular tone by sympathetic nerves or endothelin is due to specific effects of hyperinsulinemia or is secondary to general inflammatory responses associated with IR or both. Increases in responses to constrictor agents during IR apparently do not occur in all regional circulations. We have found that constrictor effects in the middle cerebral artery (28) or basilar artery (103) are unaffected in IR, but constrictor responses are enhanced in mesenteric arteries (77).

STRATEGIES TO RESTORE NORMAL VASCULAR FUNCTION IN IR

A variety of dietary, behavioral, and pharmacologic interventions have been directed toward improving vascular function by reversing or lessening the severity of IR, by delaying the progression to NIDDM, and by directly targeting the vasculature to restore normal responsiveness. Nonpharmacologic approaches involve weight loss (6, 38, 44, 66, 72, 102, 115), consumption of a balanced diet rich in antioxidants (38, 44, 66, 72, 102), and regular exercise (6, 38, 60, 72). Although these approaches have shown some benefit against IR in people and in animal models, it is unclear whether these interventions alone will lead to sustained restoration of normal responsiveness of the vasculature (6), especially with long-standing IR, and therefore more research is needed for alternative therapies (6, 37, 44, 112). Another concern is whether these approaches can be sustained for extended periods in aging individuals with other conditions that may interfere with maintaining regular physical activity or adhering to a special diet.

Several pharmacologic agents, which offer the benefits of rapid improvement, convenience, and sustained benefit, have been shown to be effective in improving vascular function in IR. For example, administration of ROS scavengers, such as superoxide dismutase and catalase, is able to restore normal vascular responsiveness by endothelium and VSM almost immediately in rodent models of IR (17, 26, 27) (Figs. 1 and 2). It also has been shown that increased dietary intake of appropriate antioxidants is an effective treatment in people against a variety of vascular-related problems (43, 87, 111). General appreciation exists of the health-related value of increasing the body level of diet-derived antioxidants (43, 87, 111). These agents are readily available in natural foods and over-the-counter supplements, and especially the water-soluble ones have few significant side effects, even with prolonged consumption. Furthermore, oral administration of the eNOS cofactor, BH_4, also restores endothelium function in an animal model of IR, probably by favoring NO production rather than superoxide anion formation (100, 101). Endothelium-dependent dilator effects also are improved with topical application of PKC inhibitors in IR rats, although IR-dependent suppression of VSM potassium channel function is not restored (27) (Figs. 1 and 2). However, the relation between PKC activation, ROS availability, and vascular reactivity in IR is complex (2, 61, 84, 88, 106). It may not be practical or beneficial to administer agents to augment BH_4 levels or to block activation of PKC for long periods because of unproven effectiveness and specificity.

Other promising pharmacologic approaches currently in widespread clinical use involve administration of insulin-sensitizing drugs, statins, or drugs acting against the renin–angiotensin system. Metformin and thiazolidinediones have been shown to improve endothelial function in experimental animals and people and to restore NO-dependent dilation (15, 23, 54, 71, 73, 82, 112), probably by promoting improvement in the IR condition (112). Statins are effective in restoring vascular function in IR in rats (18, 22, 29, 45, 78, 112) perhaps by reducing vascular inflammation and decreasing vascular levels of ROS (18, 29, 38, 78) or promoting expression of enzymes involved in the synthesis of dilator stimuli (18, 22) rather than by reducing cholesterol levels in blood. We have shown that treatment with a clinical dose of a statin in fructose-fed or Zucker obese rats is able to restore coronary and cerebral artery function (29, 78). Another pharmacologic approach that has been shown to be beneficial, especially in diabetes, involves targeting the renin–angiotensin system. Obesity, which is a major risk factor for the development of IR, leads to increased sympathetic nervous system activity and production of angiotensin II–forming enzymes and subsequent arterial hypertension and organ damage (8, 89, 98). Administration of angiotensin-converting enzyme inhibitors and angiotensin type-1 receptor blockers have been shown to reduce arterial hypertension and also to protect the heart and kidneys (8, 89, 93, 98).

An insidious and largely unappreciated aspect of IR is that detrimental effects on the cardiovascular system are taking place for a substantial period before the detection of the disease. Traditional diagnostic factors, such as fasting blood glucose levels and arterial blood pressure, may be within normal limits during much of the progression of IR. Impairment of vascular function during this period, which may interfere with coupling between metabolism and blood flow, may lead to reduced exercise tolerance and cognitive function. Insulin resistance appears to be a risk factor for Alzheimer disease (39, 58, 67, 90, 96, 113), and chronic IR has been associated with organ damage in people (14, 19, 94). Furthermore, the combination of arterial hypertension with IR or NIDDM represents an especially serious challenge to the cardiovascular system and will greatly increase the risk of atherosclerosis, coronary occlusive disease, and strokes in these patients. Therefore, young people with risk factors for IR, such as family history and obesity, should likely be more aggressively tested and treated for IR before the development of long-term complications.

PERSPECTIVES

Insulin resistance leads to impairment of normal vascular function and therefore is a major risk factor for development of cardiovascular disease. Vascular dysfunction caused by IR, at least in experimental animals, involves effects of augmented ROS produced within the vessel wall through a number of possible metabolic pathways including NAD(P)H oxidase. More research is needed in defining the specific mechanisms of impairment, especially with respect to potassium channels in VSM. Although reduced endothelium and VSM effects are reversed by ROS scavengers in animals after weeks or months of IR, it is not clear whether vascular dysfunction associated with prolonged IR, as occurs in people, would be so easily remedied. Behavioral, dietary, and/or pharmacologic approaches that prevent or reverse the underlying inflammatory process have great potential for minimizing vascular impairment and subsequent development of cardiovascular diseases associated with IR. However, additional research must be done in defining strategies for treatment in patients with long-standing IR or NIDDM.

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ABBREVIATIONS

K_{ATP} channel, ATP-sensitive potassium channel; EDHF, endothelium-derived hyperpolarizing factor; K_{Ca} channel, calcium-activated potassium channel; eNOS, endothelial nitric oxide synthase; K_{ir} channel, inwardly rectifying potassium channel; IR, insulin resistance; NAD(P)H oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NIDDM, non–insulin-dependent diabetes mellitus; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species; BH_4, (6*R*)-5,6,7,8-tetrahydrobiopterin; VSM, vascular smooth muscle; K_v potassium channels, voltage-sensitive potassium channel; ZDF rats, Zucker diabetic fatty rats; ZL rats, Zucker lean rats; ZO rats, Zucker obese rats.

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