Insulin-induced Activation of Atypical Protein Kinase C, but Not Protein Kinase B, Is Maintained in Diabetic (ob/ob and Goto-Kakazaki) Liver

CONTRASTING INSULIN SIGNALING PATTERNS IN LIVER VERSUS MUSCLE DEFINE PHENOTYPES OF TYPE 2 DIABETIC AND HIGH FAT-INDUCED INSULIN-RESISTANT STATES*

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Insulin resistance in type 2 diabetes is characterized by defects in muscle glucose uptake and hepatic overproduction of both glucose and lipids. These hepatic defects are perplexing because insulin normally suppresses glucose production and increases lipid synthesis in the liver. To understand the mechanisms for these seemingly paradoxical defects, we examined the activation of atypical protein kinase C (aPKC) and protein kinase B (PKB), two key signaling factors that operate downstream of phosphatidylinositol 3-kinase and regulate various insulin-sensitive metabolic processes. Livers and muscles of three insulin-resistant rodent models were studied. In livers of type 2 diabetic non-obese Goto-Kakazaki rats and ob/ob-diabetic mice, the activation of PKB was impaired, whereas activation of aPKC was surprisingly maintained. In livers of non-diabetic high fat-fed mice, the activation of both aPKC and PKB was maintained. In contrast to the maintenance of aPKC activation in the liver, insulin activation of aPKC was impaired in muscles of Goto-Kakazaki-diabetic rats and ob/ob-diabetic and non-diabetic high fat-fed mice. These findings suggest that, at least in these rodent models, (a) defects in aPKC activation contribute importantly to skeletal muscle insulin resistance observed in both high fat feeding and type 2 diabetes; (b) insulin signaling defects in muscle are not necessarily accompanied by similar defects in liver; (c) defects in hepatic PKB activation occur in association with, and probably contribute importantly to, the development of overt diabetes; and (d) maintenance of hepatic aPKC activation may explain the continued effectiveness of insulin for stimulating certain metabolic actions in the liver.

An unexplained paradox in insulin-resistant syndromes viz., type 2 diabetes and its frequent precursors, obesity and the metabolic syndrome, is that the liver overproduces lipids as well as glucose despite the fact that in physiological conditions insulin increases lipid production and inhibits glucose production in the liver. Accordingly, in type 2 diabetes and insulin-resistant syndromes, a priori it might be theorized that hepatic insulin resistance should result in: (a) increases in glucose production, which in fact is observed; and (b) decreases in lipid production, which is not observed. Indeed, with respect to the latter discrepancy, it is controversial as to whether increases in hepatic lipid production in insulin-resistant syndromes are caused by diminished or enhanced sensitivity to insulin. This controversy, however, is at least partly predicated by the assumption that insulin signaling mechanisms that regulate glucose and lipid metabolism in the liver fluctuate in parallel, both in health and disease.

Presently, our understanding of these seemingly paradoxical alterations in hepatic actions in insulin-resistant states is limited by the paucity of information on relevant insulin signaling mechanisms in these states. Germane to this issue, it has become increasingly clear that insulin controls metabolic processes in various target tissues largely through (a) receptor-mediated tyrosine phosphorylation of insulin receptor substrates 1 and 2 (IRS-1/2)¹ and possibly other adapter proteins, and (b) activation of IRS-1/2-dependent phosphatidylinositol 3-kinase (PI3K) and its downstream effectors, protein kinase B (PKB) and atypical protein kinase C (aPKC). During insulin action in muscle and adipocytes, it appears that both aPKC (1–5) and PKB (6–9) control glucose transport and PKB controls glucose storage in glycogen (10). During insulin action in the liver, whereas PKB promotes glycogen synthesis (11) and diminishes the availability of enzymes that increase gluconeogenesis (12) and release of glucose (13), aPKC does not appear to have major effects on hepatic glucose metabolism but, on the other hand, is required for increases in sterol regulatory element-binding protein-1c (14), a trans-activation factor that (a) increases the synthesis of a battery of enzymes that increase lipid synthesis (15), and (b) increases in livers of insulin-resistant lipodystrophic and ob/ob mice (16).

With respect to alterations in insulin signaling mechanisms in type 2 diabetes, the activation of IRS-1/2-dependent PI3K and aPKC, but not PKB, is diminished in muscle (17) and adipocytes (18) of type 2 diabetic Goto-Kakazaki (GK) rats and muscles of pre-diabetic and type 2 diabetic monkeys (19) and humans (20–22). On the other hand, the effects of insulin on

¹ The abbreviations used are: IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; aPKC, atypical protein kinase C; GK, Goto-Kakazaki.
activation of PKB and aPKC in diabetic liver are largely unknown. In the current studies, we have shown that, distinctly different from what occurs in muscle, insulin-induced activation of PKB, but not aPKC, is diminished in the livers of type 2 diabetic non-obese GK rats and ob/ob obese diabetic mice. We have also shown that the activation of both PKB and aPKC by maximally effective concentrations of insulin is normal in muscle. Thus, high GK-diabetic rat livers, which at least initially causes insulin resistance, but not diabetes. Our findings provide a reasonable explanation for the paradox of how certain hepatic effects of insulin may be maintained or enhanced, whereas other effects may be diminished in type 2 diabetes and other insulin-resistant states. They also suggest that defects in insulin signaling to aPKC are confined to skeletal muscle in lipid-induced insulin resistance, and defective activation of PKB in liver is seen with the development of diabetes.

**EXPERIMENTAL PROCEDURES**

**Experimental Rodents**—Wistar rats were obtained from Harlan Industries and served as non-diabetic controls for GK-diabetic rats. GK-diabetic rats were obtained from a colony housed at the James A. Haley Veterans Medical Center Vivarium for the past 10 years (see Refs. 17, 18, 21). These GK-diabetic rats were originally developed by repeated inbreeding of glucose-intolerant Wistar rats. Ob/ob mice and their control ob-heterozygote mice were obtained from Jackson Laboratories. C57Bl6 mice used in the studies of high fat versus standard chow feeding were obtained from Harlan Industries.

Rats and mice (males, 8–12 weeks of age) were housed in a controlled environment of alternating 12-hour light and dark cycles and fed ad libitum a standard chow diet (Harlan Teklad 20/18 with 5% fat) or, where indicated, a high fat diet (Harlan Teklad T01064 with 20% by weight anhydrous milk fat and 1% corn oil) for 3–4 weeks prior to experimental use. In some cases, GK-diabetic rats were treated with rosiglitazone, 4 mg/kg body weight for 14 days (kindly supplied by GlaxoSmithKline; Greenhouse, MA) as described in Refs. 17 and 18. All experimental procedures were fully approved by the Institutional Animal Care and Use Committee of the University of South Florida College of Medicine and the James A. Haley Veterans Administration Medical Research and Development Committee.

**Muscle and Liver Signaling Studies**—Experiments were conducted from 10 a.m.–noon. Rats and mice were injected with 1 milligram of insulin/gm body weight intramuscularly 15 min before sacrifice. As described (17–19, 21), vastus lateralis muscle and liver were rapidly removed and homogenized in ice-cold buffer that contained 0.25 M sucrose, 20 mM Tris/HCl (pH 7.5), 2 mM EDTA, 2 mM EGTA, 1 mM phenylmethylsulfonyl fluoride, 20 μg/ml leupeptin, 10 μg/ml aprotinin, 2 mM Na3VO4, 2 mM Na2VO3, 2 μM NaF, and 1 μM microcystin, after low speed centrifugation for 10 min at 700 g to remove debris, nuclei, and floating fat, the resulting cell lysates were frozen in liquid nitrogen, stored at −70°C, and subsequently immunoprecipitated with antibodies that target (a) aPKC (rabbit polyclonal antiserum from Santa Cruz Biotechnology; recognizes the C termini of both PKC-ζ and PKC-λ; (b) PKB (mouse monoclonal antibodies obtained from Upstate Biotechnology, Inc.); or (c) IRS-1 (rabbit polyclonal antiserum from Upstate Biotechnology). Immunoprecipitates were prepared, collected on Sepharose-AG beads and PI3K, PKB or PKC/ζ assay as described below. Lysates were also used to measure levels of immunoreactive proteins as described below.

**Immunoprecipitation**—aPKC activity was measured as described (1, 2, 17–19, 21). In brief, aPKCs were immunoprecipitated from cell lysates with a rabbit polyclonal antiserum (Santa Cruz Biotechnology) that recognizes the C termini of both PKC-ζ and PKC-λ (mouse adipocytes and muscle contain mainly PKC-λ and little PKC-ζ, but mouse liver contains substantial amounts of both PKC-ζ and PKC-λ), collected on Sepharose-AG beads (Santa Cruz Biotechnology), and incubated for 8 min at 30°C in 100 μl of buffer containing 50 mM Tris/HCl (pH 7.5), 100 μM Na3VO4, 100 μM Na2VO3, 1 mM NaF, 100 μM phenylmethylsulfonyl fluoride, 4 μg phosphatidylserine (Sigma), 50 μM γ-[32P]ATP (PerkinElmer Life Sciences), 5 mM MgCl2, and, as substrate, 40 μM serine analogue of the PKC-ζ pseudosubstrate (BioSource). After incubation, 50% of the substrate was trapped on P-81 filter papers and counted. Note that assays of knock-out and wild-type samples were conducted simultaneously.

**PKB Activation**—PKB enzyme activity was measured using a kit obtained from Upstate Biotechnology as described (17–19, 21). In brief, PKB was immunoprecipitated with mouse monoclonal antibodies, collected on Sepharose-AG beads, and incubated according to the directions in the PKB assay kit. PKB activation was also assessed by immunoblotting for phosphorylation of serine 473 (see below).

**PI3K Activation**—IRS-1-dependent PI3K activity was determined as described (17–19, 21). In brief, IRS-1 immunoprecipitates were examined for incorporation of 32P into PI-3-P, which was purified by thin layer chromatography and quantified with a Bio-Rad molecular analyst phosphorimaging system.

**Immunoblot Studies**—Western analyses were conducted as described (1, 2, 17–19, 21) using the following: (a) rabbit polyclonal anti-PKC-ζ antiserum (obtained from Santa Cruz Biotechnology); (b) rabbit polyclonal anti-PKB antiserum (obtained from Upstate Biotechnology); and (c) rabbit polyclonal anti-phospho-serine-473-PKB antiserum (obtained from New England Biolabs, Inc.).

**RESULTS**

**Studies in GK-diabetic Rats**—Non-obese type 2 diabetic GK rats are known to have (a) defects in insulin-stimulated glucose transport in isolated muscle (24) and adipocytes (18, 25), and (b) in euglycemic/hyperinsulinemic clamp studies, decreases in glucose disposal and uptake into muscle and adipose tissues and increases in hepatic glucose output (23, 26). This model of type 2 diabetes is probably initiated by a partial defect in insulin secretion that results in hyperglycemia-induced insulin resistance [note the reversibility of the signaling defect in aPKC activation with restoration of euglycemia as well as by thiazolidinedione (rosiglitazone) treatment (see Ref. 17), followed by moderate, albeit insufficient (i.e. relative to increases in serum glucose) increases in serum insulin. We previously reported that insulin activation of IRS-1-dependent PI3K and PKB, but not PKC, is diminished in vastus lateralis muscle and adipocytes of GK-diabetic rats (17, 18).

Presently, we found that insulin provoked a 2-fold increase in aPKC activity in both muscles and livers of non-diabetic Wistar control rats (Fig. 1). As reported previously, aPKC activation was markedly impaired in muscles of GK-diabetic rats (Fig. 1). In marked contrast to decreases in aPKC activation in muscle, the activation of aPKC was not significantly diminished in livers of GK-diabetic rats (Fig. 1). In further note, although rosiglitazone treatment fully reversed the defect in insulin-stimulated aPKC activation in muscles of GK-diabetic rats (in agreement with previously reported results; see Ref. 17), there were no significant changes in liver aPKC activation (Fig. 1).

Much different from the maintenance of normal aPKC activation, the phosphorylation and enzymatic activation of PKB was markedly diminished in livers of GK-diabetic rats (Fig. 2). This defect in hepatic PKB activation contrasts with the normal activation of PKB in muscles of GK-diabetic rats (Fig. 2). Of further note, unlike the improvement in aPKC activation in muscle (see above), rosiglitazone did not improve the defect in PKB activation in livers of GK-diabetic rats (Fig. 2).

**Studies in ob/ob Mice**—In a second study, we used (a) ob/ob mice, in which leptin deficiency leads to obesity, insulin resistance, and a type 2 diabetic syndrome, and (b), for comparison, ob-heterozygote lean control mice. Similar to findings in GK-diabetic rats, the activation of IRS-1-dependent PI3K (Fig. 3) and aPKC (Fig. 4) was markedly diminished in muscles of ob/ob mice. Somewhat different from GK-diabetic rats, PKB activation was diminished in muscles of ob/ob mice (Fig. 3), possibly reflecting a more severe defect in IRS-1-dependent PKB activation in ob/ob mice compared with GK-diabetic rats (see Ref. 17). Similar poor activation of IRS-1-dependent PI3K has also previously been observed in muscles of ob/ob mice (27). In striking contrast to alterations in muscles of ob/ob mice, but similar to findings in livers of GK-diabetic rats, the phosphorylation and enzymatic activation of PKB, but not aPKC, was diminished in livers of ob/ob mice (Fig. 5).
From the findings described above, it may be surmised that in the presently studied models of both obesity-dependent and obesity-independent type 2 diabetes, PKB, but not aPKC, activation is markedly defective in liver, whereas aPKC, with or without PKB, activation is markedly defective in muscle. In view of the dichotomy between aPKC and PKB activation in the liver and in view of the similarity of decreases in PKB activation in livers of diabetic rodents, it was important to find that the activation of neither PKB (Fig. 6) nor aPKC (Fig. 7) was compromised in livers of high fat-fed mice that are insulin-resistant but not diabetic. As in GK-diabetic rats and ob/ob mice, the apparently normal activation of aPKC in livers of high fat-fed mice contrasted with the marked defect in aPKC activation in muscles of these mice (Fig. 7). In this regard, note that in other studies we found that there are defects in insulin-stimulated glucose transport and activation of IRS-1-dependent PI3K and PKB, as well as aPKCs, in muscles of high fat-fed mice. Also note that high fat-fed mice are not hyperglycemic, suggesting that defective action of insulin in muscle does not necessarily cause hyperglycemia, and hyperinsulinemia in high fat-fed mice effectively compensates to control hepatic glucose output, which is probably the major determinant of serum glucose levels (see 28).

**DISCUSSION**

Insulin resistance in type 2 diabetes and its forerunners, obesity and the metabolic syndrome, is characterized by defects in insulin signaling in target tissues. In insulin-resistant skeletal muscle, the activation of aPKC, but not PKB, by maximally effective doses of insulin has been found to be diminished in type 2 diabetic GK rats (17), monkeys (19), and humans (20–22). Moreover, this defect in muscle aPKC activation is associated with, and probably contributes importantly to, impaired glucose uptake into muscle and diminished whole body glucose disposal in response to insulin, as seen in these diabetic states (17, 19–22). In the present study, we have shown that this consistently observed paradigm of diminished insulin-induced aPKC activation in the face of undiminished or in some cases, as in ob/ob mice, diminished PKB activation in muscle is not present in the livers of insulin-resistant diabetic rodents. Thus, aPKC activation by insulin was found to be fully or nearly fully maintained in the livers of GK-diabetic rats and ob/ob-diabetic mice, whereas PKB activation was markedly compromised in these diabetic livers. Accordingly, it seems clear that the presence of signaling defects in one target tissue does not imply that similar defects exist in other target tissues. This tissue specificity may help to explain why some effects of insulin in type 2 diabetes, particularly in the liver, may be diminished, whereas other effects may be maintained.

The maintenance of apparently normal insulin-induced activation of aPKC in the liver in each of three different forms of insulin resistance in rodents is perhaps the most unexpected finding of the present studies. This maintenance of hepatic aPKC signaling is particularly interesting because aPKCs have
been found to play an important role in mediating insulin-induced increases in sterol regulatory element-binding protein-1c (14), a trans-activation factor that controls the synthesis of a number of enzymes that are important in regulating hepatic lipid synthesis (15, 16). Accordingly, the maintenance of normal insulin-sensitive aPKC signaling in the liver, coupled with substantial increases in serum insulin levels, may be relevant to findings of increases in sterol regulatory element-binding protein-1c observed in livers of ob/ob mice (16) and development of hepatosteatosis and hyperlipidemia in high fat-fed mice.

Defects in PKB activation in liver most likely contributed importantly to hyperglycemia in GK-diabetic rats and ob/ob mice. This inference seems justified, because (a) knockout of PKBβ in mice results in increases in hepatic glucose output and development of a type 2 diabetic syndrome (29), and (b) PKB is thought to play an important role in inhibiting gluconeogenesis (12) and glucose release (13) and in increasing glycogen synthesis (11) in the liver. On the other side of the coin, the apparently normal activation of PKB in the liver of high fat-fed mice may have played an important role in maintaining normal blood glucose levels in these mice.

It may be noted that in keeping with the normal activation of PKB and aPKC in livers of high fat-fed mice is the fact that insulin-induced activation of both IRS-1- and IRS-2-dependent PI3K has been reported to be, if anything, enhanced in livers of high fat-fed rats (30). Similarly, we have observed no defect in...
IRS-1- or IRS-2-dependent PI3K activation in livers of high fat-fed mice. The fact that insulin signaling to aPKC and PKB was maintained in liver of high fat-fed mice is surprising because hepatic insulin resistance and increased glucose output have been observed in high fat-fed animals (31). Accordingly, it is possible that high fat feeding-induced hepatic insulin resistance may reflect alterations in the availability within the liver or the delivery to the liver of metabolites, e.g. free fatty acids (see Ref. 32), rather than defects in insulin signaling.

The mechanism responsible for the dichotomy between insulin-induced PKB and aPKC activation in the livers of high fat-fed mice is uncertain. With respect to PKB, its activation by insulin is substantially diminished in livers of mice in which IRS-1 (33) has been knocked out by homologous recombination methods. Interestingly, this diminution in PKB activation occurs in the face of a relatively small decrease in total insulin-induced phospho-tyrosine-dependent PI3K activation in livers of IRS-1 knock-out mice (34), suggesting the presence of substantial residual insulin-sensitive PI3K activators. It is also important to note that PKB activation by insulin is diminished in IRS-2-deficient immortalized mouse hepatocytes (35). Thus, it appears that PKB activation in the liver is dependent on both IRS-1 and IRS-2. Such dual dependence may be interpreted as suggesting that IRS-1 and -2 have different, as well as overlapping, effects on PI3K activation. However, in marked contrast to PKB, the activation of aPKC by insulin is fully intact in livers of IRS-1 knock-out mice. Thus, aPKC activation in the liver appears to be functionally independent of IRS-1. Of further note, aPKC activation, like PKB activation, is diminished in IRS-2-deficient immortalized mouse hepatocytes (35). Accordingly, it may be surmised that aPKC activation by insulin in the liver is largely dependent on IRS-2 and perhaps other PI3K activators, but not on IRS-1.

The dependence on IRS-1 of insulin-stimulated PKB, but not aPKC, activation in the liver as judged from findings in IRS-1 knock-out mice seems to offer a reasonable explanation for the marked diminution of PKB, but retention of aPKC, activation in livers of GK-diabetic rats and ob/ob mice. In keeping with this explanation, IRS-1-dependent PI3K activation is known to be deficient in livers of ob/ob mice (27). On the other hand, this explanation also requires postulating that a sufficient modicum of IRS-2-dependent PI3K or other factor-dependent PI3K activation is maintained in these insulin-resistant rodents. However, in this regard, IRS-2-dependent PI3K, like IRS-1-dependent PI3K, activation is deficient in livers of ob/ob mice (27); accordingly, there is no evidence to suggest that IRS-2-dependent PI3K activation is preferentially maintained in livers of ob/ob mice. The concomitant decreases in IRS-1- and -2-dependent PI3K activities in ob/ob liver (27) therefore raise the possibility that there may be as yet unidentified factors that influence the coupling of IRS-1- and/or IRS-2-dependent PI3K to aPKC and PKB activation, or activators of PI3K different from IRS-1 and -2 may be important for maintaining aPKC activation in livers of ob/ob and GK-diabetic mice. In this regard, note that increases in IRS-1-, IRS-2-, and pY-dependent PI3K activity in the liver are only observed during the first few minutes and, in our experience, are not seen after 10 min of

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3 M. L. Standaert, M. P. Sajan, A. Miura, Y. Kanoh, and R. V. Farese, unpublished observations.

4 M. L. Standaert, M. P. Sajan, A. Miura, Y. Kanoh, C. R. Kahn, and R. V. Farese, unpublished observations.
insulin treatment; thus, our knowledge of factors that control the activation of PI3K and PI3K-dependent signaling factors in the liver still appears to be rudimentary.

Finally, as alluded to above, although defects in the activation of aPKC and PKB by insulin in muscle do not necessarily lead to the development of overt diabetes, e.g. as seen in earlier phases of high fat-feeding in mice and rats, it seems clear that these defects in insulin signaling in muscle are important determinants of systemic insulin resistance and the development of at least certain components of the metabolic syndrome. Accordingly, it is tempting to postulate that: (a) defects in insulin actions on IRS-1, aPKC, and in some cases, PKB, in muscle can lead to hyperinsulinemia and resultant increases in hepatic lipid synthesis; (b) overt diabetes may be seen only after there is a significant defect in insulin secretion, coupled with an associated defect in the ability of insulin to activate PKB in the liver; and (c) because of continued activation of aPKCs in the liver, hepatic lipid synthesis may be maintained or increased with hyperinsulinemia in type 2 diabetes and antecedent insulin-resistant syndromes. These postulations, if confirmed, may provide a basis for development of strategies to treat the metabolic syndrome and type 2 diabetes.

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