A Role for Ceramide, but Not Diacylglycerol, in the Antagonism of Insulin Signal Transduction by Saturated Fatty Acids*

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Multiple studies suggest that lipid oversupply to skeletal muscle contributes to the development of insulin resistance, perhaps by promoting the accumulation of lipid metabolites capable of inhibiting signal transduction. Herein we demonstrate that exposing muscle cells to particular saturated free fatty acids (FFAs), but not mono-unsaturated FFAs, inhibits insulin stimulation of Akt/protein kinase B, a serine/threonine kinase that is a central mediator of insulin-stimulated anabolic metabolism. These saturated FFAs concomitantly induced the accumulation of ceramide and diacylglycerol, two products of fatty acyl-CoA that have been shown to accumulate in insulin-resistant tissues and to inhibit early steps in insulin signaling. Preventing de novo ceramide synthesis negated the antagonistic effect of saturated FFAs toward Akt/protein kinase B. Moreover, inducing ceramide buildup recapitulated and augmented the inhibitory effect of saturated FFAs. By contrast, diacylglycerol proved dispensable for these FFA effects. Collectively these results identify ceramide as a necessary and sufficient intermediate linking saturated fats to the inhibition of insulin signaling.

The peptide hormone insulin stimulates the uptake and storage of glucose in skeletal muscle and adipose tissue while simultaneously inhibiting its efflux from the liver. In certain pathological conditions, including Type 2 diabetes mellitus (1) and metabolic syndrome X (2), these tissues become resistant to insulin such that a maximal dose of the hormone is unable to elicit these anabolic responses. Numerous studies suggest that the oversupply of lipid to peripheral tissues might contribute to the development of this insulin resistance. First, insulin-resistant subjects frequently display signs of abnormal lipid metabolism. These saturated FFAs concomitantly induced the accumulation of ceramide and diacylglycerol, two products of fatty acyl-CoA that have been shown to accumulate in insulin-resistant tissues and to inhibit early steps in insulin signaling. Preventing de novo ceramide synthesis negated the antagonistic effect of saturated FFAs toward Akt/protein kinase B. Moreover, inducing ceramide buildup recapitulated and augmented the inhibitory effect of saturated FFAs. By contrast, diacylglycerol proved dispensable for these FFA effects. Collectively these results identify ceramide as a necessary and sufficient intermediate linking saturated fats to the inhibition of insulin signaling.

The insulin receptor is a heterotetrameric tyrosine kinase receptor that mediates all of the anabolic effects of insulin (19). The activated receptor phosphorylates intracellular docking molecules (termed insulin receptor substrates, or IRS proteins) that recruit and stimulate multiple different effector enzymes (20). Phosphatidylinositol (PI) 3-kinase is a target of IRS proteins that is an obligate intermediate in the metabolic, anti-apoptotic, and mitogenic effects of insulin (21). PI 3-kinase phosphorylates specific phosphoinositides to generate phosphatidylinositol-3,4-biphosphate, and phosphatidylinositol-3,4,5-trisphosphate, which subsequently recruit cytosolic serine/threonine kinases phosphoinositide-dependent kinase-1 and Akt/protein kinase B (PKB) to the plasma membrane. The association between these phosphoinositides and the Akt/PKB pleckstrin homology domain promotes Akt/PKB activation by facilitating its phosphorylation on two regulatory residues (i.e. Ser-473 and Thr-308) (22). Studies in cultured cells involving the overexpression of constitutively active (23) or dominant negative (24, 25) forms of Akt/PKB coupled with experiments involving the microinjection of inhibitory anti-Akt/PKB antibodies (26) indicate the involvement of the enzyme in the regulation of anabolic metabolism. Moreover, knockout mice lacking the Akt2/PKBβ isoform develop a diabetes-like syndrome characterized by insulin resistance in both skeletal muscle and liver (27).

The molecular mechanisms linking FFAs to the inhibition of insulin action remain unclear. In 1963, Randle et al. (28) proposed the existence of a glucose-fatty acid cycle by which glucose and lipids could serve as competitive substrates for oxidation in muscle. More recent studies in either cultured cells (9–11) or rodent models of obesity and/or insulin resistance (29, 1-phenyl-2-decanoylamino-3-morpholino-1-propanol; HOK cells, human embryonic kidney cells; DMEM, Dulbecco’s modified Eagle’s medium; CMV, cytomegalovirus; PP2A, protein phosphatase 2A.

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¶ The abbreviations used are: FFA, free fatty acid; IRS, insulin receptor substrate; PI, phosphatidylinositol; PKB, protein kinase B; DAG, diacylglycerol; GSK3β, glycogen synthase kinase 3β; PDMP, n-threo-
30), however, indicate that fatty acids also disrupt one or more early steps in insulin signal transduction. As shown herein, the saturated fats palmitate and stearate, but not their mono-unsaturated counterparts oleate and palmitoleate, blocked insulin activation of Akt/PKB while concomitantly promoting the accumulation of ceramide and diacylglycerol in C2C12 myotubes. These lipid metabolites have both been shown to accumulate in tissues from insulin-resistant rodents (31) and to inhibit insulin signal transduction in cultured cells (32–37). Specifically, studies with short chain ceramide analogs reveal that ceramide prevents insulin activation of Akt/PKB (32–34), whereas investigations with phorbol esters, which mimic the effects of diacylglycerol (DAG), indicate that DAG blocks upstream signaling events by promoting the serine phosphorylation of IRS-1 (38–42). Using various methods for manipulating either the synthesis or breakdown of ceramide, we found that endogenously produced ceramide was both sufficient and necessary for the inhibition of insulin signaling by palmitate. Moreover, we determined that DAG was dispensable for the inhibitory palmitate effects. These findings implicate ceramide as a potentially important intermediate linking saturated fats to the development of insulin resistance.

EXPERIMENTAL PROCEDURES

Reagents—C2-recognized and α-threo-1-Phenyld-2-decanoylamino-3- morpholino-1-propanol (PDM) were obtained from Calbiochem, okadaic acid was from Invitrogen, fetal bovine serum was from Atlas Biologicals (Fort Collins, CO), and silica gel 60 thin layer chromatography (TLC) plates from Merck. The following additional reagents were obtained from Sigma: palmitate, stearate, oleate, palmitoleate, Dulbecco’s modified Eagle’s medium (DMEM), fatty acid free bovine serum albumin, C-6 ceramide, C-18 ceramide, humentin B1, myriocin, cycloserine, and N-oleoylthanolamine. Antibodies utilized included rabbit polyclonal anti-phospho-Akt (Ser-473) and anti-phospho-glycerol synthase kinase 3β (GSK3β) (serine 9) antibodies from Cell Signaling, mouse anti-glycerol synthase kinase 3β (GSK3β) antibody from Transduction Labs (Lexington, KY), rabbit anti-phosphor-mitogen-activated protein kinase antibody from Promega (Madison, WI), rabbit polyclonal anti-Akt, and horseradish peroxidase-conjugated anti-rabbit and anti-mouse antibodies from Santa Cruz Biotechnology (Santa Cruz, CA).

Cell Culture—C2C12 myoblasts were maintained at 37°C in DMEM containing 10% fetal bovine serum. For differentiation into myotubes, the myoblasts were grown to confluency, and the medium was replaced with DMEM containing 10% horse serum. Myotubes were used for experiments 4 days after differentiation.

FFA Treatment—Free fatty acids were administered to cells by conjugating them with FFA-free bovine serum albumin. Briefly, FFAs were dissolved in ethanol and diluted 1:100 in 1% FBS-DMEM containing 2% (w/v) bovine serum albumin. Two hours before performing the experiments, myotubes were placed in serum-free-DMEM containing 2% bovine serum albumin in either the presence or absence of FFAs.

Immunoblot Analysis—Cell lysates were resolved by SDS-PAGE, transferred to nitrocellulose, and immunoblotted using methods described previously (43). Detection was done using the Enhanced Chemiluminescence or the Enhanced Chemiluminescence Plus kit from Amersham Biosciences according to the manufacturer’s instructions.

Results

To identify specific FFAs capable of antagonizing insulin signal transduction, we evaluated the effect of specific saturated and monounsaturated FFAs on insulin-stimulated Akt/ PKB phosphorylation and activation in C2C12 myotubes. Palmitate (C16:0) and stearate (C18:0), which comprise greater than 90% of the saturated FFAs in human serum (46), each markedly inhibited insulin stimulation of Akt/PKB phosphorylation (Fig. 1A). By contrast, neither oleate (C18:1), which makes up 80% of the circulating monounsaturated pool (46), nor palmitoleate (C16:1), had any effect (Fig. 1A). Palmitate and stearate also inhibited insulin-stimulated phosphorylation...
of GSK3β (Fig. 1A), a substrate of Akt/PKB with numerous functions including the regulation of glycogen synthase activity (44). Palmitate inhibited Akt/PKB phosphorylation within 2–4 h (Fig. 1B) at a FFA concentration as low as 0.25 mM (Fig. 1C). This concentration is comparable with that found physiologically (9) and is similar to that used in prior studies evaluating FFA effects in both immortalized muscle cells (9, 10) and isolated skeletal muscle strips (11). Neither palmitate nor stearate inhibited IRS1-associated PI 3-kinase (Fig. 2).

We next determined whether the inhibitory FFAs also induced the accumulation of DAG and/or ceramide. Briefly, DAG kinase can phosphorylate both DAG and ceramide to produce phosphatidic acid and ceramide 1-phosphate, respectively, which can be resolved by TLC. When the reaction is allowed to proceed in the presence of [32P]ATP, the phosphorylated products can be detected using a Storm PhosphorImager (47). As shown in Fig. 3, palmitate and stearate induced ceramide accumulation 3-fold over basal levels (Fig. 3A), whereas they induced DAG accumulation 6- and 3.5-fold, respectively (Fig. 3B). By contrast, neither oleate nor palmitoleate had any effect on either ceramide or DAG accumulation. Interestingly, another saturated FFA, myristate (14:0), induced DAG synthesis while having no effect on ceramide accumulation or Akt/PKB or GSK3β phosphorylation (data not shown).

As described earlier, ceramide blocks insulin signaling by preventing the activation of Akt/PKB (9, 32), whereas DAG inhibits “upstream” signaling events (i.e. insulin stimulation of IRS-1-associated PI 3-kinase (38–42)). Because palmitate also inhibited Akt/PKB but not PI 3-kinase (Fig. 2), we hypothesized that ceramide and not DAG was the principal effector linking saturated FFAs to the inhibition of Akt/PKB. To test this hypothesis, we determined whether inhibitors of de novo ceramide synthesis could prevent palmitate inhibition of insulin signaling. Briefly, ceramide biosynthesis requires the coordinate action of two enzymes, i.e. serine palmitoyltransferase and ceramide synthase (for review, see Ref. 48). Serine palmitoyltransferase catalyzes the initial step, which involves the condensation of serine and palmitoyl-CoA to form 3-ketosphinganine, a sphingolipid that is subsequently reduced to form the sphingoid base sphinganine. Ceramide synthase catalyzes sphinganine acylation, producing dihydroceramide, which is then converted to ceramide by the introduction of a trans-4,5 double bond in the sphinganine moiety. Pretreating C2C12 myotubes with myriocin, a fungal toxin that inhibits serine palmitoyltransferase, completely prevented the palmitate-induced increase in ceramide levels (Fig. 4A) but had no effect on DAG accumulation (Fig. 4B). As predicted, myriocin completely negated the inhibitory effect of palmitate on both Akt/PKB and GSK3β phosphorylation (Fig. 5A). Similarly, cycloserine, another serine palmitoyltransferase inhibitor, also reversed the palmitate effect on Akt/PKB phosphorylation (Fig. 5B). Fumonisin B1, a fungal toxin that inhibits ceramide synthase, also prevented the palmitate effect on ceramide (Fig. 4A), but not DAG (Fig. 4B), accumulation. Like myriocin and cycloserine, fumonisin B1 protected both Akt/PKB and GSK3β from the

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**Fig. 2.** Palmitate and stearate do not inhibit IRS1-associated PI 3-kinase activity. C2C12 myotubes were incubated in the presence or absence of the indicated fatty acids (16 h, 0.75 mM) before stimulation with insulin (Ins, 100 nM, 10 min). IRS-1 was immunoprecipitated from cell lysates and incubated with [32P]ATP and phosphoinositide. Lipids were extracted and resolved by thin layer chromatography. Phosphoinositide 3-phosphate (PI(3)P) produced by the phosphorylation of phosphoinositide by PI 3-kinase was visualized using a Storm PhosphorImager. Data are representative of three independent experiments.

**Fig. 3.** Palmitate and stearate stimulate both ceramide and diacylglycerol accumulation. Lipid extracts from C2C12 myotubes were incubated with DAG kinase and [32P]ATP as described under “Materials and Methods.” Lipids were then re-extracted, resolved by thin layer chromatography, and detected using a Storm PhosphorImager. A and B demonstrate the levels of ceramide and DAG, respectively, in cells treated with or without the indicated fatty acids (16 h, 0.75 mM). Ceramide and DAG levels are presented as the mean fold increase (over basal) ± S.E. Asterisks denote that the values obtained were significantly different from basal levels ($p \leq 0.05$).
the ceramidase inhibitor glucosylceramide synthase inhibitor PDMP) or deacylation (palmitate alone (Fig. 6), and both drugs markedly inhibited Treating C2C12 myotubes with either compound increased ceramide levels by blocking its normal route(s) of metabolism (50).

Pounds were shown previously to increase endogenous ceramide by exogenous C2-ceramide (data not shown). By increasing ceramide glucosylation or deacylation, could actually augment the palmitate effect on ceramide instead blocks the insulin-stimulated translocation of Akt/PKB to the plasma membrane (32, 33). To test whether the effects of palmitate required PP2A in C2C12 myotubes, we pretreated cells with okadaic acid before treating with insulin. In the presence of okadaic acid, palmitate did not prevent insulin-stimulated Akt/PKB phosphorylation (Fig. 6A). Neither drug affected the expression of Akt or GSK3β (data not shown). Thus, increasing endogenous ceramide levels by an alternative mechanism recapitulated the inhibitory effects of palmitate on Akt/PKB phosphorylation. We next attempted to determine whether these drugs, by blocking ceramide glucosylation or deacylation, could actually augment the palmitate effect on either the accumulation of long chain ceramides or the antagonism of insulin signaling. As predicted, the inclusion of either PDMP or N-oleoyethanolamine along with palmitate potentiated the effects of either reagent individually on both ceramide accumulation (Fig. 6A) and the inhibition of Akt/PKB phosphorylation (Fig. 6, C and D). Ceramide has been shown to prevent Akt/PKB activation by at least two independent mechanisms. In certain cell types, okadaic acid, an inhibitor of protein phosphatase 2A (PP2A), negates the antagonistic effects of ceramide on Akt/PKB. This finding suggests that ceramide blocks insulin action by accelerating the rate of Akt/PKB dephosphorylation (34, 51, 52). In other cell types, however, okadaic acid has no effect, and ceramide instead blocks the insulin-stimulated translocation of Akt/PKB to the plasma membrane (32, 33). To test whether the effects of palmitate required PP2A in C2C12 myotubes, we pretreated cells with okadaic acid before treating with insulin. In the presence of okadaic acid, palmitate did not prevent insulin-stimulated Akt/PKB phosphorylation (Fig. 7A). However, because okadaic acid stimulated Akt/PKB phosphorylation in the absence of insulin we could not distinguish between (a) okadaic acid reversing the effect of palmitate or (b) okadaic acid stimulation of Akt/PKB being insensitive to ceramide. To more definitively determine whether palmitate was working through PP2A, we used recombinant adenovirus to overexpress the SV40 small T antigen. This protein was shown previously to inhibit PP2A activity by displacing one of the regulatory subunits of the enzyme (53). SV40 small T expression com-

**Fig. 4.** Myriocin and fumonisin B1 prevent palmitate stimulation of ceramide synthesis. C2C12 myotubes were incubated in the presence or absence of palmitate (0.75 mM), myriocin (10 μM), or fumonisin B1 (FB1, 50 μM) for 16 h before lipid extraction. Ceramide and DAG levels were quantified as in Fig. 3. Ceramide and DAG levels are presented as the mean fold increase (over basal) ± S.E. Asterisks denote that the value was significantly different from basal levels (p ≤ 0.05).

**Fig. 5.** Myriocin, cycloserine, and fumonisin B1 prevent the inhibition of insulin signaling by palmitate. C2C12 myotubes were incubated in the presence or absence of palmitate (8 h, 0.75 mM) before stimulation with insulin (100 nM, 10 min). Selected samples were treated with or without the serine palmitoyltransferase inhibitors PaI, myriocin (10 μM), or cycloserine (1 mM) or the ceramide synthase inhibitor fumonisin B1 (FB1, 50 μM) just before adding palmitate. Cell lysates were resolved by SDS-PAGE, transferred to nitrocellulose, and immunoblotted with the indicated antibodies. Detection was by enhanced chemiluminescence. Data are representative of at least four independent experiments. P, phospho-.
pletely prevented the effects of both palmitate and C2-ceramide on Akt/PKB phosphorylation (Fig. 7B), confirming the likely involvement of PP2A in the inhibitory effects of saturated FFAs in C2C12 myotubes.

**DISCUSSION**

The strong correlation between intramyocellular triglyceride levels and the severity of insulin resistance suggests that lipid oversupply to peripheral tissues could cause or exacerbate the condition. Many researchers have hypothesized that one or more derivatives of fatty acyl-CoA are likely to link inappropriate fat deposition in skeletal muscle to the inhibition of insulin signaling (6). Possible products of long chain acyl-CoA capable of inhibiting insulin signaling include ceramide and DAG (for review, see Ref. 18), but a definitive role for neither has been established. The data presented herein indicate that endogenously produced ceramide is both capable of inhibiting Akt/PKB and, more importantly, is necessary for the inhibitory effects of saturated FFAs. First, palmitate, stearate, and C2-ceramide blocked insulin signaling at the same step (i.e. by blocking activation of Akt/PKB but not stimulation of PI 3-kinase (Figs. 1 and 2)) (9). Second, inhibiting de novo ceramide synthesis completely prevented palmitate induction of ceramide synthesis and its antagonism of Akt/PKB and GSK3β phosphorylation (Figs. 4 and 5). Third, preventing ceramide metabolism and/or degradation recapitulated the effects of palmitate on both intracellular ceramide accumulation and the inhibition of insulin signaling (Fig. 6). Fourth, blocking ceramide metabolism while concomitantly adding palmitate augmented its effect on both ceramide accumulation and the inhibition of Akt/PKB phosphorylation (Fig. 6). And fifth, expressing the SV40 small T antigen, an inhibitor of PP2A, prevented the effects of both C2-ceramide and palmitate on Akt/PKB phosphorylation (Fig. 7). Collectively these data implicate ceramide in insulin resistance resulting from the oversupply of saturated FFAs to skeletal muscle.

To manipulate intracellular ceramide levels in these experiments, we relied on the use of a large number of enzyme inhibitors to block ceramide synthesis or degradation. To minimize the possibility that our observations were the result of nonspecific pharmacological effects, we employed inhibitors capable of blocking separate enzymes in the various pathways. For example, the fungal toxins myriocin and fumonisin inhibit separate enzymes that are required for de novo ceramide synthesis (i.e. serine palmitoyltransferase and ceramide synthase, respectively) (48), and both protected C2C12 myotubes from
the inhibitory effects of palmitate. Cyclooxygenase, a serine palmitoyltransferase inhibitor that is structurally dissimilar to myriocin, also prevented the antagonistic effects of palmitate. These compounds did not affect Akt/PKB expression or activation in the absence of FFAs (data not shown), and none were capable of blocking the antagonistic effects of exogenously added C2-ceramide, which presumably bypasses the site of action of these inhibitors (data not shown). To induce ceramide accumulation we also used unique compounds with separate intracellular targets. Both PDMP and N-oleoylthanolamine, by inhibiting glucosylceramide synthase and ceramidase, respectively, were able to induce ceramide accumulation and to block Akt/PKB activation (Fig. 6). Thus, by using a broad array of inhibitors, our data conclusively indicate that ceramide is both a necessary and sufficient intermediate linking palmitate to the antagonism of insulin signaling.

Although ceramide proved to be required for the effects of palmitate, the DAG derived from saturated FFAs was incapable of inhibiting insulin signaling to Akt/PKB. Specifically, in Figs. 4 and 5 we demonstrate conditions where insulin signaling was inhibited despite the fact that DAG accumulation was not. The hypothesized involvement of DAG in insulin resistance derives from multiple prior studies both in cultured cells and rodents. For example, treating various cell lines with phorbol esters, which mimic the effects of DAG, inhibits insulin signaling to IRS-1 (38–41) and Akt (42). Moreover, several PKC isoforms including PKCo (54, 55), -b1 and -b2 (56), -g (55), and - (38) are downstream effectors of DAG that purportedly antagonize insulin signaling by phosphorylating IRS-1 on inhibitory serine residues. Observations that DAG levels are often elevated in rodent models of insulin resistance (for review, see Ref. 57) have fueled speculation that the lipid levels are often elevated in rodent models of insulin resistance will be necessary to determine the extent to which this lipid metabolite contributes to the pathologies associated with the condition.

CONCLUSIONS

Numerous studies implicate saturated fats, particularly palmitate, in the development of insulin resistance. First, palmitate is one of the most abundant FFAs found in skeletal muscle as well as being one of the most prevalent acyl chains found in the diglyceride fraction of lipid extracts (64). Second, an inverse relationship exists between the consumption of palmitate and insulin sensitivity (65, 66). And third, insulin-resistant muscles demonstrate accelerated rates of palmitate uptake (67). A similar cadre of results suggests that the over-accumulation of ceramide could participate in the development of insulin resistance. First, various rodent models of insulin resistance, including Zucker fa/fa rats (31) and mice overexpressing lipoprotein lipase (16), demonstrate elevated intramuscular ceramide levels. Second, exercise training Wistar rats improves insulin sensitivity while markedly lowering intramuscular ceramide levels (68). And third, short chain ceramide analogs inhibit insulin-stimulated Akt/PKB activation and/or glucose uptake in 3T3-L1 adipocytes (32, 35), brown adipocytes (34), C2C12 and L6 myotubes (9, 33), and isolated rat skeletal muscle (69). The experiments described herein clearly indicate that endogenously produced ceramide is not only capable of antagonizing insulin action but, more importantly, is required for the inhibitory effects of long chain saturated fatty acids on insulin signaling. Although aberrant ceramide accumulation is unlikely to account entirely for the diverse array of defects found in insulin resistant tissues, the findings presented herein implicate ceramide as a potentially important mediator of the deleterious effects of long chain saturated fats. Studies attempting to block ceramide synthesis in various animal models of insulin resistance will be necessary to determine the extent to which this lipid metabolite contributes to the pathologies associated with the condition.

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