Glucose-dependent Regulation of Cholesterol Ester Metabolism in Macrophages by Insulin and Leptin*

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Insulin resistance, obesity, and diabetes are characterized by hyperglycemia, hyperinsulinemia, and hyperleptinemia and are associated with increased risk of atherosclerosis. In an effort to understand how this occurs, we have investigated whether these factors cause dysregulation of cholesterol ester metabolism in J774.2 macrophages. Raising glucose levels alone was sufficient to increase uptake of acetylated low density lipoprotein but did not stimulate synthesis of cholesterol ester. In the presence of high glucose, both insulin and leptin increased the rate of cholesterol ester synthesis, although they did not further increase uptake of acetylated low density lipoprotein. However, in the presence of high glucose both insulin and leptin caused a significant increase in the activity of acyl-CoA: cholesterol O-acyltransferase (ACAT) combined with a significant reduction in the level of hormone-sensitive lipase (HSL). Because ACAT is the main enzyme responsible for cholesterol ester synthesis and HSL contributes significantly to neutral cholesterol ester hydrolysis activity, this suggests that glucose primes the J774.2 cells so that in the presence of high insulin or leptin they will store cholesterol esters. This contrasts with 3T3-L1 adipocytes, where HSL activity and expression are increased by insulin in high glucose conditions. These findings may provide an explanation for the observation that in conditions characterized by hyperglycemia, hyperleptinemia, and hyperinsulinemia, triglyceride lipolysis in adipocytes is increased while hydrolysis of cholesterol esters in macrophages is decreased, contributing to foam cell formation.

Atherosclerosis-related disorders are the principle cause of death in the Western world, and insulin resistance, type-2 diabetes, and obesity are well recognized risk factors for coronary heart disease. Individuals in these categories have a 2–3-fold increased risk of developing macrovascular heart disease (1–5). Insulin resistance, type-2 diabetes, and obesity are characterized by hyperleptinemia, hyperinsulinemia, and hyperglycemia, suggesting these may be acting as proatherogenic factors (6–8). Indeed, there is good evidence that regulation of HSL is likely to play an important role in determining CE levels in cells, and it is}

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1 The abbreviations used are: CEs, cholesterol esters; ACAT, acyl-CoA:cholsterol O-acyltransferase; LDL, low density lipoprotein; acLDL, acetylated LDL; nCEH, neutral cholesterol ester hydrolase; HSL, hormone-sensitive lipase; PBS, phosphate-buffered saline.
therefore important to understand the mechanisms affecting the activity of this enzyme.

The effects of glucose, insulin, and leptin on the mechanisms regulating CE metabolism in macrophages have not been well studied. Indeed there are no reports of effects of these factors on LDL uptake or ACAT activity in macrophages, although the recent finding that increasing glucose concentrations cause an increase in the expression of the CD36 scavenger receptor indicates that hyperglycemia might have a direct role in stimulating LDL uptake (22). However, we have recently reported that insulin and leptin acutely stimulate HSL activity in J774.2 macrophages (23), suggesting they may have a regulatory role in CE metabolism in these cells. Recent data also suggest chronic exposure of cells to glucose and insulin is also likely to have effects on HSL gene expression because insulin and glucose regulate lipidolysis and HSL expression in adipocytes (24, 25) and glucose increases HSL expression in pancreatic β-cells (26). Therefore we have investigated whether glucose levels, in combination with high levels of insulin or leptin, might effect CE synthesis in macrophages and whether there are detectable effects on cholesterol uptake, ACAT activity, or HSL activity in these cells.

EXPERIMENTAL PROCEDURES

Reagents—125I-Protein A, cholesterol-[1-14C]oleate, [1-14C]oleic acid and [1-14C]oleoyl-CoA were obtained from Amersham Biosciences. Diacylated LDL was purchased from Intracel. RPMI 1640 and newborn calf serum were obtained from Invitrogen. Fetal calf serum and Dulbecco’s modified Eagle’s medium were from Sigma. Anti-HSL antibody was kindly supplied by Dr. Raj Beri, Astra Zeneca, Macclesfield, UK. Leptin was obtained from Biogenes Ltd. All other reagents used were from Sigma.

Cell Culture and Stimulations—The murine macrophage cell line J774.2 was grown in RPMI medium (2 g glucose/l) supplemented with 10% fetal calf serum (heat-inactivated at 50 °C for 30 min) and antibiotics antimycotic. 3T3-L1 adipocytes were cultured and differentiated as previously described (27). Where serum starvation was necessary, J774.2 macrophages were incubated overnight in serum-free RPMI media containing 0.2% bovine serum albumin (fatty acid-free) and appropriate levels of glucose. Experiments were performed on confluent J774.2 cells.

Immunoprecipitation and Western Blotting—After stimulation with leptin (10 nM) or insulin (1 μM) in 5 or 20 mM glucose, the cells were washed once with ice-cold PBS (calf-to-magnesium-free) and lysed in buffer containing 1% Triton X-100, 10 mM Tris base (pH 7.4), 5 mM EDTA, 0.1 mM sodium orthovanadate, 10 μg/ml leupeptin, 1 μg/ml pepstatin, and 200 μl milliliter-inactivating units of aprotinin. Cell lysates were precipitated at 4 °C with 125I-HSL antibody before incubation with protein A-agarose (HSL) for a further hour. For Western blotting, samples were subject to SDS-polyacrylamide gel electrophoresis, then transferred onto polyvinylidene fluoride and immunoblotted with appropriate primary antibodies and bands visualized with 125I-protein A using a Fuji FLA2000 PhosphoImager. Bands were quantitated using the Fuji ImageQuant software.

LDL Uptake—For acetylated LDL uptake experiments, cells were incubated in RPMI containing either 5 or 20 mM glucose, with or without the addition of 1 μM insulin or 10 mM leptin, for 24 h at 37 °C. The for the last 4 h of the incubation, 10 μg/ml fluorescent Dil-labeled acLDL was added. Cells were washed three times in PBS before fluorescence was measured using a Fuji FLA 2000 fluorescent image analyzer.

Neutral Cholesterol Esterase (nCEH) (nCEH/HLS) Activity Assay—To measure nCEH activity in J774.2 lysates, cell monolayers were washed with PBS before being scraped into 200 μl of assay buffer (5 mM imidazole, pH 7.0, 30% glycerol, 50 mM NaCl, 20 mM EDTA, 0.1 mM benzamidine, 1 mM dithiothreitol, 5 μg/ml leupeptin, 1 μg/ml pepstatin, 200 kallikrein-inactivating units of aprotinin). Cells were lysed by 4 rounds of freeze-thawing followed by centrifugation at 14000 rpm at 4 °C. Activity was assayed as described previously (28). To measure nCEH activity in anti-HSL immunoprecipitates, 50 μl of assay buffer was added to the beads, and activity was assayed. [1-14C]Oleic acid released from labeled cholesterol[1-14C]oleate was quantitated by scintillation counting. One unit of enzyme activity catalyzes the release of 1 μmol of oleate per minute. We found that activity in HSL immunoprecipitates correlates very well with activity in total cell lysates under all conditions investigated (data not shown).

ACAT Activity Assay—The ACAT assay was performed according to the method of Mazière et al. (29, 30) with some modifications. Briefly, following serum starvation and treatment with insulin (1 μM) or leptin (100 nM) for 24 h in low or high glucose RPMI, J774.2 cells were washed twice in PBS and scraped into 20 mM potassium phosphate buffer, pH 7.4, followed by homogenization using a micropestle. The ACAT assay mixture contained 150 μg of protein, 0.1 μCi of [1-14C]oleoyl-CoA diluted with 0.1 μCi unlabelled oleoyl-CoA, 5 mM MgCl2, and 0.1 M potassium phosphate buffer, pH 7.4, in a total volume of 80 μl. Incubations were performed for 5 min at 37 °C. The reaction was stopped on ice. Radioactivity in cholesterol esters was separated by thin layer chromatography on silica gel plates developed in hexane/diethyl ether/acidic acid (70:30:2) and analyzed using a Fuji FLA2000 PhosphoImager. Spots were quantitated using the Fuji ImageQuant software. [1-14C]Cholesteryl olate was used as standard.

Acetylated LDL Cell Loading—Human lipoproteins were isolated by density gradient ultracentrifugation in a vertical rotor, as previously described (31). LDL was acetylated by the addition of saturated sodium acetate solution followed by acetic anhydride (32). Prior to loading, cells were serum starved overnight. Cells were washed twice in PBS before the addition of RPMI containing either 5 or 20 mM glucose and either 1 μM insulin or 10 mM leptin, 100 μg/ml acetylated LDL, and 1 μCi/ml [1-14C]oleate-0.12% bovine serum albumin and incubation for 24 h. Cells were washed twice in PBS and harvested into 0.5 ml of PBS. 0.5 ml of chloroform/methanol (2:1) was added followed by vortexing for 10 s before centrifugation at 1800 × g for 10 min at 10 °C. The lower organic phase was transferred to a glass vial, and the upper phase was washed with chloroform/methanol as before. Again the lower organic phase was transferred to the glass vial. Chloroform was removed by drying under nitrogen. Lipids were resuspended in isopropanol and separated by thin layer chromatography on silica gel plates developed in hexane/ethyl ether/acidic acid (80:20:1, v/v/v). Radioactive bands were detected and quantitated using a Fuji FLA2000 PhosphoImager, and bands were quantitated using the Fuji ImageQuant software. Recovery efficiencies were determined using tritiated standards and were 98.4% for cholesterol ester, 93.4% for cholesterol, and 87.6% for triglyceride.

RESULTS

Effects of Glucose, Leptin, and Insulin on Cholesterol Ester Synthesis—We investigated the effects of leptin, insulin, and glucose on CE metabolism in macrophages. J774.2 macrophages were incubated with acetylated LDL and [1-14C]oleate, and the amount of label incorporated into CEs was determined following a 24-h incubation with insulin or leptin. These experiments were performed at both 5 and 20 mM glucose to determine whether glycemia affected CE formation. We find that increasing glucose levels in the media did not alter the formation of CE over the 24-h period (Fig. 1). Further, in 5 mM glucose insulin does not affect CE formation in the macrophages, although in 20 mM glucose insulin does cause a clear increase in CE formation (Fig. 1B). This indicates the increase in glucose levels acts to potentiate the effects of insulin and leptin on CE formation.

Effect on Modified LDL Uptake—To determine whether the increase in CE content of macrophages is due to increased uptake of modified LDL, Dil-labeled acLDL was used to measure uptake under the same conditions (Fig. 2). Incubation of macrophages in high glucose media results in more acLDL uptake compared with low glucose media, but there was no significant stimulation by insulin or leptin, suggesting the effect on the rate of CE synthesis described above required control of the enzymes that regulate cholesterol ester synthesis and degradation.
Effect on ACAT Activity—We then investigated the effects of leptin, insulin, and glucose on ACAT activity to determine whether the increase in CE synthesis would correlate with an increase in ACAT activity. ACAT activity was determined by measuring \([14C]\text{oleoyl-CoA}\) incorporation into CE. To verify that this represented true ACAT activity, assays were performed in the presence of 100 nM 447C88, a known ACAT inhibitor, and this was found to completely abolish activity (data not shown). As expected, ACAT activity was induced in J774.2 cells incubated for 24 h with acLDL both at low and high glucose levels (data not shown). To test the effects of glucose, leptin, and insulin, J774.2 macrophages were incubated for 24 h with insulin (1 \(\mu\)M) or leptin (10 nM) at 5 or 20 mM glucose. At 5 mM glucose, insulin increased ACAT activity ~6-fold, whereas leptin did not affect ACAT activity (Fig. 3). Increasing glucose levels alone did not significantly affect ACAT activity, but both insulin and leptin significantly induced ACAT activity at 20 mM glucose (~9-fold compared with basal levels at low glucose) (Fig. 3).

Effect on Neutral Cholesterol Esterase Activity—We also investigated effects on neutral cholesterol esterase activity, focusing on nCEH activity associated with HSL, because there is strong evidence that HSL acts as an nCEH in macrophages (19, 33). In J774.2 macrophages, HSL also accounts for a large percentage of the cellular neutral cholesterol esterase activity, as demonstrated by the fact that immunodepletion of HSL reduces nCEH activity in cell lysates by over 50% while reducing HSL protein levels by a similar amount (Fig. 4). This indicates that changes in HSL expression or activity could contribute to alterations in the levels of CE in these cells. To test whether this was the case, J774.2 macrophages were exposed to insulin or leptin in the presence of 5 or 20 mM glucose for up to 24 h, and HSL activity and expression were determined. Changes in glucose alone had no effect on HSL activity...
HSL activity has been most extensively studied in adipocytes, where it has been reported that insulin and high glucose increase triglyceride lipolysis (24) and HSL expression (25). This would suggest that, unlike macrophages, HSL activity and/or expression is increased under these conditions in adipocytes. Therefore we investigated the effect of insulin and high glucose on HSL expression and activity in 3T3-L1 adipocytes. As predicted, insulin caused a sustained increase in HSL activity and expression in high glucose, and no effect was seen in low glucose (Fig. 7).

**DISCUSSION**

The results of the current study demonstrate that under normoglycemic conditions neither insulin nor leptin promote cholesterol ester deposition in macrophages. However, we identify a novel mechanism by which increases in glucose levels become permissive for insulin and leptin to stimulate cholesterol ester synthesis. Such a mechanism has important implications because atherosclerotic heart disease is closely associated with obesity, insulin resistance, and type-II diabetes in humans and atherosclerosis is often evident before diabetes is diagnosed (1–5, 10, 34). We have identified glucose-dependent effects on three of the major processes regulating cholesterol metabolism that are all likely to contribute to the increased rate of cholesterol ester accumulation.

The first of these is increased uptake of modified LDL stimulated by high glucose. Two mechanisms have previously been identified by which glucose could increase acLDL uptake. In the first it has recently been shown (22) that glucose increases expression of the CD36 scavenger receptor. A second explanation may lie in the observation that CD36 can act as a receptor for advanced glycation endproducts (AGE) (35). Incubation media containing 20 mM glucose would be expected to create more AGE than media containing 5 mM glucose, and therefore increased uptake into the cell by both CD36 and the scavenger receptor class A types I and II is likely. However, the increase in acLDL uptake induced by glucose alone does not correlate with an increase in cholesterol ester accumulation, so the increased uptake of acLDL alone is not sufficient to increase the rate of cholesterol ester accumulation.
The second possible mechanism investigated involves changes in ACAT activity. Surprisingly, we find that insulin and leptin both stimulate ACAT activity. Insulin stimulates ACAT activity 5–6-fold in low glucose and causes a similar level of activation at high glucose, whereas the leptin effect is only 2-fold in low glucose but is similar to that of insulin in high glucose. We believe that the increased ACAT activity is likely because of increased ACAT expression, given the fact that this effect is observed after 24 h. Any such changes are likely to be in the ACAT1 form because this is most highly expressed in macrophages (16, 36), and at least in liver this form is regulated by cholesterol levels (36). To date, the lack of suitable antibodies has prevented us from determining whether this is indeed the case in our system. However, our evidence indicates that the increase in ACAT activity, although likely to facilitate increased CE synthesis, is itself probably not sufficient to stimulate CE synthesis. This is shown by the finding that glucose alone increases acLDL uptake, which also stimulates ACAT activity and yet is not associated with an increase in CE synthesis under these conditions.

The third mechanism that could be contributing to cholesterol ester deposition is the rate of cholesterol ester breakdown via nCEH; we find HSL is a major nCEH in the J774.2 cells. We have previously shown (23) that following acute exposure leptin causes an increase, whereas insulin causes a decrease, in HSL activity in J774.2 macrophages in media containing 10 mM glucose. However, the previous study did not investigate the chronic regulation of HSL in macrophages by insulin, leptin, and glucose, the factors that characterize the obese and insulin-resistant states. There is evidence that the combination of insulin and glucose are important in chronically regulating HSL in other cell types. HSL activity is up-regulated in 3T3-L1 adipocytes and pancreatic β-cells exposed to high glucose levels (25, 26), whereas chronic exposure to insulin has previously been reported to increase HSL expression levels in adipocytes (37) and to increase lipid synthesis in a glucose-dependent manner in adipocytes (24). We extend the previous studies in adipocytes by showing the combined effects of insulin and glucose on lipolysis are most likely due to effects on HSL expression, because in high glucose media insulin caused a sustained increase in HSL activity and expression in 3T3-L1 adipocytes, whereas no effect was seen in low glucose.

However, the regulation of HSL expression and activity in
macrophages is clearly different from that in adipocytes and β-cells. Chronic exposure of cells to insulin, and in particular leptin, in low glucose slightly increased HSL expression and activity, which agrees with our previous findings (23). This would tend to protect macrophages from increases in lipid accumulation. In the case of leptin, this fits with the hypothesis that one of the physiological roles of leptin is to prevent lipid accumulation in peripheral cells (38). Although increases in glucose concentrations had no direct effect on HSL expression, they did act to prime the cells such that addition of leptin or insulin caused a reduction in HSL expression and activity. Therefore, glucose acts synergistically with leptin or insulin to down-regulate HSL activity in macrophages. This effect is most likely an effect on expression rather than alterations in post-translational modification-induced changes in intrinsic activity because the changes in activity correlate closely with the changes in level of protein. The down-regulation would certainly act to promote CE accumulation in J774.2 macrophages. We have recently found that HSL is expressed at readily detectable levels in human macrophages (data not shown), meaning that these findings are also likely to have relevance in cholesterol ester metabolism in humans.

In summary, our findings demonstrate that a combination of hyperglycemia and hyperinsulinemia or hyperleptinemia stimulates CE synthesis in J774.2 macrophages. We have also identified three mechanisms by which high glucose levels play a permissive role in this process: increased uptake of modified LDL, increased ACAT activity, and decreased nCEH activity associated with HSL. This contrasts with adipocytes where HSL is up-regulated in the presence of high glucose and insulin. These findings could explain why lipolysis is increased in adipocytes in the insulin-resistant state, and circulating free fatty acid levels rise while cholesterol ester hydrolysis in macrophages is apparently reduced. The finding that these effects of insulin and leptin were only observed in the presence of glucose concentrations corresponding to hyperglycemia in vivo is particularly interesting because this could explain why foam cell formation is particularly accelerated in insulin-resistant individuals and why death from ischemic heart disease correlates closely with blood glucose levels (10). Therefore, this identifies a previously unrecognized mechanism that if present in human macrophages could contribute to the increased incidence of atherosclerosis in insulin resistant, obese, and diabetic subjects.

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