To investigate the mechanism of glucocorticoid-induced lymphocytolysis, we used two-dimensional gel electrophoresis to analyze the effect of dexamethasone on the synthesis of individual proteins in S49 mouse lymphoma cells. We found that synthesis of a 78-Kd protein is preferentially maintained following dexamethasone treatment, at a time when the synthesis of most other cellular proteins is decreased. Synthesis of this protein could also be induced by tunicamycin, suggesting that it might be the 78-Kd glucose-regulated protein (GRP78). The identity of the 78-Kd protein with GRP78 was confirmed by limited chymotryptic mapping and immunoprecipitation analysis. Preferential synthesis of GRP78 in dexamethasone-treated cells was not secondary to alterations in the glycosylation of cellular proteins. Significantly, steady-state levels of GRP78 mRNA were unchanged following dexamethasone treatment. Preferential synthesis of GRP78 in glucocorticoid-treated S49 cells may reflect the unique property of GRP78 mRNA to be translated under conditions that interfere with the translation of most other cellular mRNAs. GRP78 is a highly conserved protein that is essential for cell viability. Preferential synthesis of GRP78 may be a protective response to metabolic events that interfere with normal mRNA translation in glucocorticoid-treated mouse lymphoma cells.

MATERIALS AND METHODS

Materials. Acrylamide and other chemicals for gel electrophoresis were from Bio-Rad, Richmond, CA. Molecular weight standards were from Pharmacia LKB Biotechnology, Uppsala, Sweden. Dexamethasone, α-chymotrypsin, and other chemicals were from Sigma, St Louis, MO. [35S]methionine (1,100 Ci/mmol) was from ICN Radiochemicals, Plainview, NY, and (α32P)dCTP (6,000 Ci mmol) was from New England Nuclear, Boston, MA. Transcription and translation kits and rabbit reticulocyte lysates were from Promega, Madison, WI. The random primed DNA labeling kit was from Boehringer-Mannheim, Mannheim, Germany.

Cell culture. The glucocorticoid-sensitive S49 24.3.2 cell line, a T-cell lymphoma line derived from an induced lymphoma in the BALB/c mouse,29 was purchased from the Cell Culture Facility, University of California, San Francisco. The glucocorticoid-resistant S49 derivatives, S49.22r and S49.143r, were given by Dr Keith Yamamoto, University of California, San Francisco. Cells were cultured in complete medium (Dulbecco's modified Eagle's medium supplemented with 2 mmol/L glutamine, 50 U/mL penicillin, 50 µg/mL streptomycin, 0.4 mmol/L nonessential amino acids, and 10% [vol/vol] heat-inactivated horse serum) at 37°C in a 7% CO2 atmosphere and diluted into fresh medium three times per week to maintain a maximum cell density below 1.5 million cells/mL.

Cell treatment and labeling. Dexamethasone, dissolved in ethanol and diluted into complete medium, was added to cells to give from the Department of Medicine, Case Western Reserve University School of Medicine and Ireland Cancer Center, University Hospitals of Cleveland, Cleveland, OH.

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the final concentrations specified in the Results; an equivalent amount of ethanol in complete medium was added to untreated cells. Tunicamycin, dissolved in 0.1 mol/L NaOH, was added to cells to give a final concentration of 0.75 μmol/L; an equivalent amount of vehicle was added to untreated cells. Cells were then incubated at 37°C for various periods of time before labeling with (35S)methionine or isolating RNA. For labeling, cells were gently pelleted and resuspended in complete medium lacking methionine; (35S)methionine was then added to give a final concentration of 50 μCi/mL and the cells were incubated for an additional 30 minutes at 37°C.

**Gel electrophoresis.** Two-dimensional gel electrophoresis, using isoelectric focusing in the first dimension followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) in the second dimension, was according to O'Farrell modified as described. The first-dimension isoelectric focusing gels contained equal amounts of pH 5 to 8 ampholytes (Bio-Rad), pH 5 to 7 ampholytes, pH 3 to 10 ampholytes (Pharmacia LKB Biotechnology), and pH 3.5 to 10 ampholytes (Bio-Rad), totaling a final concentration of 4% (wt/vol). After labeling, cells were pelleted and resuspended in solubilization buffer (9 mol/L urea, 2% [vol/vol] NP-40, 8% [wt/vol] pH 3 to 10 ampholytes, 2% [vol/vol] β-mercaptoethanol). The amount of (35S)methionine-labeled protein in cell extracts was determined by measuring the amount of trichloroacetic acid–precipitable radioactivity. Equal amounts of (35S)methionine-labeled protein were applied to each gel in a given experiment. Gels were stained with Coomassie Blue dye and destained before drying onto filter paper under vacuum. Dried gels were exposed to Kodak XAR-5 film (Eastman Kodak, Rochester, NY) at −80°C. Autoradiograms were scanned using a Bio-Rad Model 620 Video Densitometer and data was normalized according to the intensity of the spot corresponding to the 70-Kd protein from three separate two-dimensional gels, combined, and loaded into a sample well of a second SDS-PAGE. At the same time, spots corresponding to the protein of interest were excised from three separate two-dimensional gels, combined, and loaded into a sample well of the second SDS-PAGE. Buffer (0.125 mol/L Tris, pH 6.8, 0.1% SDS, 1 mmol/L EDTA, 10% [vol/vol] glycerol, and 0.001% [wt/vol] bromphenol blue) containing a-aminotryptophan (50 μg/mL) was added to the sample wells. Electrophoresis was performed at 20 mA constant current until the tracking dye crossed the interface between the 5% stacking gel and the 14% running gel, at which point the power was interrupted for 30 minutes, and then resumed until the tracking dye reached the bottom of the running gel. Gels were dried and subjected to autoradiography as described above.

**Immune precipitation of GRP78.** Cytosol preparation and immune precipitation were according to previously published methods. After treatment with either dexamethasone or tunicamycin, and labeling with (35S)methionine as described above, cells were lysed by resuspension and incubation for 15 minutes at 4°C in the following buffer: 50 mmol/L Tris, pH 7.4, 150 mmol/L NaCl, 10 mmol/L glucose, 2 IU hexokinase, 10 mmol/L iodoacetamide, 1% Triton-X100. The sample was then centrifuged at 14,000 × g for 20 minutes at 4°C, and the concentration of radiolabeled protein in the clear supernatant cytosol was measured by trichloroacetic acid precipitation. Cytosol samples containing equivalent amounts of radiolabeled protein were incubated for 60 minutes at 4°C with either a monoclonal antibody to GRP78 provided by Dr David Bole (University of Michigan, Ann Arbor, MI), or an equivalent concentration of a control monoclonal IgG (Sigma). Immunoreactive proteins were adsorbed to goat anti-mouse IgG-agarose and analyzed by SDS-PAGE according to previously described methods, with the only modification being that the wash buffer contained 10 mmol/L Tris, pH 7.4, 150 mmol/L NaCl, and 0.1% Triton X-100.

**Immune precipitation of cathepsin D.** S49 cells were suspended in methionine-free culture medium supplemented with 10 μCi/mL (35S)methionine and incubated with or without 1 μmol/L dexamethasone or 0.75 μmol/L tunicamycin for 4 hours at 37°C. Cells were then washed twice with phosphate-buffered saline and the cell pellet was suspended in an equal volume of lysis buffer (25 mmol/L Tris, pH 8.0, 1 mmol/L EDTA, 50 mmol/L NaCl, 10% glycerol, 0.5% deoxycholic acid, 0.5% NP-40). The cell suspension was frozen for 5 minutes in liquid nitrogen and then thawed on an ice-water bath for 10 minutes. The sample was then centrifuged at 10,000 × g for 20 minutes at 4°C. The clear supernatant cytosol was incubated for 60 minutes with a rabbit antiseraum (final dilution, 1:27) to human placent catshepsin D, provided by Dr Stuart Kornfeld, Washington University, St Louis, MO. Immunoreactive proteins were adsorbed to protein A-sepharose and analyzed by SDS-PAGE according to previously described methods.

**Northern hybridization.** Total cellular RNA was isolated from dexamethasone-treated and untreated cells by sedimentation through cesium chloride as described. Samples containing 10 μg of RNA were electrophoresed on a 1% agarose gel and blotted onto a Zeta-Probe membrane (Bio-Rad). Membranes were simultaneously hybridized with a cDNA (pS3C5) containing the coding sequence for hamster GRP78, given by Dr Amy Lee (University of Southern California, Los Angeles), and a cDNA corresponding to CHO-B, a constitutively expressed mRNA, given by Dr Michael Wilson (Scrpps Clinic and Research Foundation, La Jolla, CA). CDNs were labeled with α-[32P]dCTP using a random primed DNA labeling kit. The prehybridization, hybridization, and washes of the membrane were performed according to the manufact
turer's standard protocol (Bio-Rad). Membranes were then exposed to Kodak XAR-5 film at −80°C.

RESULTS

S49 mouse lymphoma cells are often used as a model for the study of glucocorticoid-induced cell lysis. In the present study, we used two-dimensional gel electrophoresis to detect major changes in the synthesis of individual proteins that might occur early in the process of glucocorticoid-induced lysis of S49 cells. In previous studies of this cell line, DNA fragmentation, an early sign of glucocorticoid-induced apoptosis, was detected within 6 hours of dexamethasone exposure, and increased trypan blue dye uptake, a sign of overt cell death, was detected within 12 hours of dexamethasone exposure. Therefore, in the experiments reported here, cells were incubated with dexamethasone for a maximum of 3 to 4 hours before analysis. Following treatment with dexamethasone, cells were pulse-labeled for 30 minutes with (35S)methionine and then cell extracts were analyzed by two-dimensional gel electrophoresis. One thousand individual proteins were visualized by autoradiography. A close-up view of a portion of a typical two-dimensional gel is shown in Fig 1. We found that the spot labeled “c,” corresponding to a 78-Kd protein (pI, ~5.2), and the spot labeled “e,” corresponding to a 94-Kd protein (pI, ~5.0), were consistently more intense on gels of dexamethasone-treated samples than on gels of untreated samples. For orientation, the spot corresponding to the 70-Kd constitutive heat-shock protein, hsc70 (labeled “b”), and the spot corresponding to the 90-Kd heat-shock protein, hsp90 (labeled “d”), were identified in heat-shock experiments (not shown), while the spot corresponding to actin (labeled “a”) was identified by its relative abundance, size, and isoelectric point. The intensity of the 78-Kd spot, normalized according to the intensity of the hsc70 and actin spots, was increased by 3.2-fold ± 0.7-fold (mean ± SEM; N = 8) following dexamethasone treatment. Although close inspection of Fig 1 suggests that the intensity of spots corresponding to several other proteins, in addition to the spots corresponding to the 78-Kd and 94-Kd proteins, may be different in treated and untreated cells, these differences were not as consistently observed in multiple experiments and their significance is currently unknown.

It is important to note that protein synthesis, measured by incorporation of (35S)methionine into acid-precipitable material, was 40% to 80% (mean, 60%) less in dexamethasone-treated cells than in untreated cells and, consequently, volumes of cell extracts were adjusted so that equal amounts of (35S)methionine-labeled protein from treated and untreated cells were applied to two-dimensional gels. Therefore, the greater intensity of the 78-Kd and 94-Kd protein spots on gels from dexamethasone-treated samples compared with untreated samples (Fig 1) could be due to either preferential synthesis of these proteins under conditions in which the synthesis of most other cellular proteins is decreased, or, alternatively, preferential extraction from dexamethasone-treated cells. To exclude the latter possibility, control experiments were performed in which cells were pulse-labeled with (35S)methionine and then incubated with or without dexamethasone during a 3-hour chase with excess unlabeled methionine, followed by analysis of cell extracts by two-dimensional gel electrophoresis. In those experiments, the intensity of the 78-Kd and 94-Kd protein spots was the same on autoradiograms corresponding to dexamethasone-treated and untreated samples, indicating that these proteins were not preferentially extracted following dexamethasone treatment. We conclude that the 78-Kd and 94-Kd proteins are preferentially synthesized in dexamethasone-treated S49 cells.

The 78-Kd and 94-Kd proteins described in this study do not correspond to any of the glucocorticoid-induced proteins previously identified in normal rat thymocytes. Based on their relative molecular masses and isoelectric points, we suspected that the 78-Kd and 94-Kd proteins were GRP78 (the 78-Kd glucose-regulated protein) and GRP94 (the 94-Kd glucose-regulated protein), respectively. These proteins are typically induced by agents, such as tunicamycin, which interfere with protein glycosylation. Therefore, cells were incubated in parallel with or without dexamethasone, and with or without tunicamycin, before pulse-labeling and subsequent analysis of cell extracts by two-dimensional gel electrophoresis (Fig 2). The results indicate that the 78-Kd and 94-Kd proteins were induced by both tunicamycin and dexamethasone, providing strong evidence that these proteins are GRP78 and GRP94, respectively.

To confirm the identity of the 78-Kd protein with GRP78,
we compared it with authentic, in vitro translated GRP78 by limited chymotryptic mapping. The spot corresponding to the 78-Kd protein was excised from three two-dimensional gels, combined, and partially digested with chymotrypsin. The resulting peptides, along with a chymotryptic digest of in vitro translated GRP78, were resolved by SDS-PAGE and analyzed by autoradiography, demonstrating close correspondence between the peptide maps of the 78-Kd dexamethasone-induced protein and in vitro translated GRP78 (Fig 3). Minor differences in the peptide maps may result from differences in the relative susceptibility of in vitro versus in vivo synthesized GRP78 to chymotryptic digestion, perhaps secondary to posttranslational modifications that occur in vivo, but not in vitro.

As further evidence for the preferential synthesis of GRP78 following dexamethasone treatment, cells were incubated in parallel with or without dexamethasone, and with or without tunicamycin, for 4 hours prior to pulse-labeling with (35S)methionine, followed by immunoprecipitation of GRP78 from cell extracts. Immunoprecipitated proteins were resolved by SDS-PAGE and analyzed by autoradiography (Fig 4). The results indicate that the amount of radiolabeled GRP78 immunoprecipitated from dexamethasone-treated and tunicamycin-treated cells was greater than the amount immunoprecipitated from untreated cells. As in preceding experiments, protein synthesis was reduced following treatment with these agents and volumes of cell extracts were adjusted so that equal amounts of (35S)methionine-labeled protein were subjected to immunoprecipitation. Therefore, the results confirm that GRP78 is preferentially synthesized in dexamethasone-treated and tunicamycin-treated cells at a time when the synthesis of most other cellular proteins is decreased.

Interestingly, several proteins were found to co-immunoprecipitate with GRP78 from tunicamycin-treated cells (designated by arrowheads in Fig 4), consistent with earlier evidence that unglycosylated proteins bind stably to GRP78. However, there was no evidence for co-immunoprecipitation of proteins with GRP78 from dexamethasone-treated cells, suggesting that unglycosylated proteins do not accumulate and bind to GRP78 in dexamethasone-treated cells and that defective protein glycosylation is not responsible for preferential GRP78 synthesis in dexamethasone-treated cells. As a more direct test of the effect of dexamethasone on glycoprotein synthesis and processing in mouse lymphoma cells, we compared the effects of dexamethasone and tunicamycin on the processing of a typical lysosomal enzyme, cathepsin D. Cathepsin D was immunoprecipitated from (35S)methionine-labeled extracts of dexamethasone-treated and tunicamycin-treated S49 cells and analyzed by SDS-PAGE (Fig 5). The results demonstrate that dexamethasone, unlike tunicamycin, does not interfere with the glycosylation of cathepsin D or its maturation from abkba97-67-45-30-20-
GLUCOCORTICOID REGULATION OF GRP78/BiP SYNTHESIS

Fig 4. Immunoprecipitation of GRP78 from dexamethasone-treated and tunicamycin-treated cells. S49 cells were incubated for 4 hours with (+) or without (−) 1 μmol/L dexamethasone, and with (+) or without (−) 0.75 μmol/L tunicamycin, and then pulse-labeled with [35S]methionine for 30 minutes. Cell extracts containing equivalent amounts of trichloroacetic acid-precipitable radioactivity were immunoprecipitated either by monoclonal antibody to GRP70 or by an equivalent concentration of control IgG. Immunoprecipitated proteins were resolved by SDS-PAGE; an autoradiogram of the gel is shown. Arrowheads point to proteins that coprecipitated with GRP78.

Fig 5. Effect of dexamethasone and tunicamycin on glycosylation and processing of cathepsin D. S49 cells were incubated for 4 hours without (−) or with (+) 1 μmol/L dexamethasone, and without (−) or with (+) 0.75 μmol/L tunicamycin, in the continuous presence of [35S]methionine. Cathepsin D was then immunoprecipitated from cytosol, resolved by SDS-PAGE, and analyzed by autoradiography. Arrowheads point to the 48-Kd unglycosylated precursor, the 53-Kd glycosylated precursor, and a 51-Kd mature form. The slow-moving radioactive band located above the 97-Kd standard has been detected previously by others and is thought to represent a coprecipitating contaminant.

and in stress protection. GRP78 binds transiently to normal proteins as they are processed through the endoplasmic reticulum, but stably to malfolded or unglycosylated proteins whose transport from the endoplasmic reticulum is blocked.

Although the present study has focused on GRP78, the results also suggest that another glucose-regulated protein, GRP94, may be preferentially synthesized in glucocorticoid-treated S49 cells. Although the function of GRP94 is not understood, it is considered to be a member of the 90-Kd heat-shock protein family and represents the major calcium binding protein of the endoplasmic reticulum. GRP94 and GRP78 genes share common regulatory domains and are often coordinately regulated by common trans-acting factors.

GRP78 was first detected as one of several proteins whose synthesis is induced when cells are cultured in the absence of glucose. GRP78 synthesis is also induced by agents, such as tunicamycin, which interfere with protein glycosylation. Because decreased glucose transport is one of the earliest catabolic effects of glucocorticoid hormones on lymphoid cells, and because there is evidence that glucose starvation may result in synthesis of truncated oligosaccharides, we initially thought that the relative

a 53-Kd precursor to a 51-Kd mature form. We conclude that the effect of dexamethasone on GRP78 synthesis is not due to interference with glycoprotein synthesis or processing.

Previous studies have indicated that GRP78 is regulated primarily at a transcriptional level. Therefore, we measured GRP78 mRNA levels in dexamethasone-treated and untreated S49 cells by Northern blotting, using a GRP78 cDNA as a hybridization probe. The results show that the steady-state level of GRP78 mRNA in S49 cells was essentially unchanged following dexamethasone treatment for 1 or 3 hours (or for longer periods of time, not shown). We conclude that preferential synthesis of GRP78 in dexamethasone-treated cells is due to preferential translation of GRP78 mRNA, rather than increased GRP78 gene transcription.

DISCUSSION

Using two-dimensional gel electrophoresis to examine the synthesis of individual proteins in S49 mouse lymphoma cells, we found that the synthesis of a 78-Kd protein, which we identified as GRP78, is preserved following glucocorticoid treatment, at a time when the synthesis of most other cellular proteins is decreased. GRP78, which is identical to BiP, is a member of the 70-Kd heat-shock protein family that resides in the endoplasmic reticulum, where it participates in the folding and assembly of nascent polypeptides.
increase in GRP78 synthesis observed in glucocorticoid-treated S49 cells might be secondary to defective glycosylation of cellular proteins. However, we did not detect any effect of glucocorticoid treatment on the glycosylation and processing of a typical lysosomal enzyme, cathepsin D. Also, unlike the situation in tunicamycin-treated cells, unglycosylated proteins did not appear to bind stably to, and co-immunoprecipitate with, GRP78 in glucocorticoid-treated S49 cells. Therefore, we conclude that GRP78 induction in dexamethasone-treated lymphoid cells, unlike that occurring in tunicamycin-treated cells, cannot be directly attributed to the accumulation and binding of unglycosylated proteins to GRP78.

In addition to the wild-type, glucocorticoid-sensitive S49 cell line used in the experiments described here, we have also studied two glucocorticoid-resistant S49 mutants that have defective glucocorticoid receptors, S49.143r and S49.22r.63 Dexamethasone treatment had no effect on overall protein synthesis or on GRP78 synthesis in the mutant cells (data not shown), indicating that the changes in overall protein synthesis and GRP78 synthesis in wild-type S49 cells were mediated through the glucocorticoid receptor, a prototype transcriptional regulatory molecule.8 However, earlier studies showed that glucocorticoid hormones have no effect on GRP78 gene transcription.64 Also, in the present study, steady-state levels of GRP78 mRNA were not increased in glucocorticoid-treated cells. Therefore, the relative increase in GRP78 synthesis that accompanies glucocorticoid treatment of S49 cells indicates that GRP78 mRNA continues to be efficiently translated under conditions in which the translation of most cellular mRNAs is decreased.

Interestingly, recent studies have shown that the cellular mRNA encoding GRP78 continues to be translated in poliovirus-infected cells at a time when the translation of other cellular mRNAs is inhibited, due to inactivation of the eIF-4F complex and failure of capped cellular mRNAs to associate with polysomes.65 The 5' noncoding region of the GRP78 mRNA appears to mediate translation initiation by an internal ribosome-binding mechanism under such conditions.66 Therefore, a plausible hypothesis is that glucocorticoid treatment either directly or indirectly interferes with cap-dependent translation of most mRNAs in S49 cells, but that the translation of GRP78 mRNA is maintained through the use of an alternative, internal ribosome-binding mechanism.

Although the original intent of the present study was to identify protein synthetic changes that occur early in the process of glucocorticoid-induced lymphocytolysis, we do not yet have evidence for a direct role of GRP78 in this process. However, it is possible that preferential synthesis of GRP78 may confer an important protective function to the cell when glucocorticoid-induced metabolic changes interfere with normal mRNA translation. GRP78 has been identified as a calcium-binding protein56-59 and its synthesis increases following calcium ionophore-induced depletion of endoplasmic reticulum calcium stores.60 Mobilization of endoplasmic reticulum calcium stores by calcium ionophores depresses rates of translation initiation in various mammalian cells; subsequently, cells appear to accomodate by preferential synthesis of GRP78.68 Thus, an intriguing possibility is that a decrease in the synthesis of most cellular proteins, with the exception of GRP78, may be secondary to a glucocorticoid-induced perturbation of endoplasmic reticulum calcium stores. Consistent with this concept, glucocorticoids have previously been shown to induce a sustained increase in the cytoplasmic calcium level of lymphoid cells, a process which can be mimicked by treating cells with the calcium ionophore, A23187.28,69,70

In conclusion, GRP78 is a highly conserved protein that is essential for cell viability.71,72 Although its regulation at the transcriptional level has received considerable attention,69 translational control of GRP78 has been recognized only recently, and only in the setting of poliovirus-infected cells.65 The findings of the present study are the first to suggest that translational control of GRP78 may be of importance in maintaining GRP78 synthesis under conditions that adversely affect overall protein synthesis in glucocorticoid-treated cells. Further work will be required to specifically determine how glucocorticoids might affect the complex process of translation in mouse lymphoma cells and to define what role preservation of GRP78 synthesis...
might play in the process of glucocorticoid-induced lymphocytolysis.

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Prefential synthesis of the 78-Kd glucose-regulated protein in glucocorticoid-treated S49 mouse lymphoma cells

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