Primary cultures of rat hepatocytes were subjected to amino acid and serum deprivation for 4 h. This treatment augmented the sensitivity to ensuing hydrogen peroxide exposure for 30 min. The by nutrient deprivation-increased autophagy, ascertained by transmission electron microscopy and uptake of the lysosomotropic weak base acridine orange within the intracellular acidic vacuolar apparatus. The desferrioxamine-available pool of iron increased 2.5-fold during deprivation, compared with control cells. Furthermore, amino acid deprivation increased the cellular protein turnover, measured by radioactive labeling with \(^{3}H\)Leu. Exposure to 40 \(\mu M\) ascorbic acid specifically decreased the turnover of ferritin, as estimated by enzyme-linked immunosorbent assay, and prevented an increase of the desferrioxamine-available iron pool, resulting in protection against hydrogen peroxide-induced cell killing.

Thus, hepatocytes with nutrient deprivation-enhanced autophagy contain a larger pool of catalytically active iron than control cells. This iron pool is mainly derived from the turnover (autophagy) of cytosolic ferritin and is probably situated in the lysosomes. Furthermore, nutrient-deprived cells show augmented sensitivity to hydrogen peroxide-induced oxidative stress, since the enhanced availability of iron in low molecular weight form results in an increased potential of intralysosomal Fenton chemistry, that may cause lysosomal rupture with release of potent hydrolytic enzymes.

Iron is the most abundant transition metal in living organisms and is absorbed, transported, and stored in a controlled manner to prevent the catalytic breakdown of peroxides by ferrous iron in Fenton-like reactions (1). The bulk of iron is stored as a core of \(\text{Fe(OH)}_3\) in ferritin, and in this form it is thought to be protected from reduction (2). However, iron is required for numerous metalloenzymes and the synthesis of heme, and little is known about how iron gets from the intracellular stores to the biochemical systems involved in biosynthesis. It is generally assumed that such mobilized iron is located in an intracellular low molecular weight pool, where it is weakly chelated and thus more easily available for reducing substances to its ferrous form during, e.g. oxidative stress (1, 3). It has also been suggested that ferrous iron can be reducibly released from ferritin during oxidative stress, which makes ferritin a potentially hazardous biomolecule under pathological conditions (4–7). Release of cytoplasmic iron, presumably from ferritin, has also been shown during ischemia in isolated rat hearts, due to the accumulation of acidic products in the tissue during anaerobiosis (8). The importance of catalytically active iron in oxidative-stress-induced cell killing has been shown in several studies (9, 10). Addition of the strong iron chelator, desferrioxamine (DFX), protected against the oxidative damage induced by hydrogen peroxide (11–13) and redox cycling compounds (14).

In addition to cytosolic iron, iron also occurs in the lysosomal apparatus as a result of the autophagic degradation of iron-containing proteins (15–17). This source of low molecular weight iron, so far not very well recognized, has lately been shown to be far more active in the cell-damaging processes caused by oxidative stress than is generally believed (11, 14, 18). In this context it is noteworthy that DFX is taken up into cultured cells by endocytosis rather than by diffusion (14, 19). Consequently, DFX will be located primarily in the secondary acidic vacuolar apparatus of the cell.

Ascorbic acid was recently shown to retard the degradation of ferritin in K562 erythroleukemia cells by reducing its autophagocytic degradation (20). This effect seems to be quite specific and does not affect general protein turnover. This property of ascorbic acid was initially suggested by Bridges and Hoffman (21) to increase the availability of iron to various chelators. On the contrary, Sakai et al. (16) showed that ascorbic acid protected hepatocytes from tert-butylhydroperoxide-induced oxidative cell killing by reducing the turnover of ferritin rather than by acting as a radical scavenger.

In the present study we show that nutrient deprivation-increased autophagy in primary cultures of hepatocytes causes an increase in the intracellular pool of DFX-available iron causing an increased sensitivity to hydrogen peroxide. This probably occurs through increased turnover of ferritin, as well as other iron-containing proteins, resulting in enhanced intralysosomal iron-catalyzed oxidative reactions.

**EXPERIMENTAL PROCEDURES**

**Chemicals**—Hydrogen peroxide was purchased from Aldrich-Chemie (Steinheim, Germany); dexamethasone, diethyl maleate, type I collagen, fluorescein isothiocyanate-dextran-70, and insulin from Sigma; fetal calf serum, HEPES, glutamine, and Williams E medium from Life Technologies, Inc. Ltd. (Paisley, Scotland, UK); desferrioxamine B (deferoxamine mesylate) from Ciba-Geigy AG (Basel, Switzerland); the ATP-monitoring kit 1245–200 from BioOrbit (Turku, Finland). \(^{3}H\)Leucine was from NEN Life Science Products (Bad Homburg, Germany); and Percoll from Kabo-Pharmacia (Uppsala, Sweden). All HPLC

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1 The abbreviations used are: DFX, desferrioxamine; AO, acridine orange; DEM, diethyl maleate; FX, ferrioxamine; GSH, reduced glutathione; HPLC, high performance liquid chromatography; PBS, Dulbecco’s phosphate-buffered saline; TEM, transmission electron microscopy.

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solvents were from Fisons Scientific Equipment (Loughborough, UK) and of HPLC grade.

Isolation and Culture of Primary Rat Hepatocytes—Hepatocytes were isolated from male Wistar rats (weight 160–220 g) by collagenase perfusion and purified by centrifugation through 1.09 g/ml Percoll as described before (22). The cells were suspended in Williams E medium containing 0.335 μM dexamethasone, 10% fetal calf serum, 2 mM glutamine, and 5 μg/ml insulin and plated in plastic 35-mm Petri dishes (73,000 cells/cm²) (Costar, Cambridge, MA) precoated with 1.7 μg/cm² type I collagen or on similarly coated coverslips placed in the dish. Viability was >97% as tested by the trypan blue dye exclusion test. The cultures were incubated at 37 °C in a humidified atmosphere of 5% CO₂ in air. After 2 h of incubation, the culture medium was changed to remove unattached cells.

Amino Acid and Serum Deprivation—After 5 h in culture, the culture medium was withdrawn and phosphate-buffered saline (0.15 M NaCl, 2.7 mM KCl, 8.1 mM Na₂HPO₄, 1.5 mM KH₂PO₄, 0.9 mM CaCl₂, and 0.5 mM MgCl₂, pH 7.4, 300 mMOS) containing 5.5 mM glucose was added, and the incubation was continued for 1–4 h. Control cells were incubated in a parallel experiment in Williams complete medium. In some experiments 40 μM freshly prepared ascorbic acid, 1 mg desferrioxamine, or 0.25 mM iron(III) chloride was included in the saline during the deprivation period.

Depletion and Analysis of GSH—Glutathione was depleted by incubating cell cultures with 25 μM diethyl maleate (DEM) for 15 min in complete Williams medium. The GSH level was then comparable with the amount of GSH detected in cells nutrient-deprived for 4 h (i.e. 10.6 nmol/mg of protein).

GSH was extracted by adding 0.5 M HClO₄ containing 1 mM EDTA to Petri dishes containing 700,000 cells (23) and analyzed by HPLC fitted with an electrochemical detector as described by Honegger et al. (24). Protein analysis, according to Lowry et al. (25), was performed on the acid-solubilized pellet that was dissolved in 1.0 M NaOH.

ATP Determination—Culture medium was removed from the Petri dish and 500 μl of 2.5% (w/v) trichloric acid was rapidly added. The cells were collected and stored on ice for 10–20 min. ATP analysis was performed on a 20-μl cell lysate in 780 μl 0.1 M Tris acetate buffer (pH 7.5) containing 200 μl of ATP monitoring reagent (1243–200 BioOrbit) in a chemoluminometer (BioOrbit). The ATP content was calculated from a standard curve.

Protein Turnover—Two hours after seeding, hepatocyte proteins were labeled with [3H]Leu (60.0 Ci/mmol) in complete Williams medium for 24 h. After two washes with PBS, the labeling medium was replaced by Williams medium without serum containing 2 mM leucine. After 1 h, the cultures were washed three times with PBS and deprived for up to 4 h as described above. Triton X-100 (final concentration: 0.5%) was then added to the cultures, and the proteins were precipitated with perchloric acid (10% final concentration) and prepared as described before (16). The radioactivity in the acid-soluble and -insoluble fractions was determined by liquid scintillator counting (LKB 1217, Wallac, Finland). The net release of [3H]Leu-labeled protein during the 4-h incubation was expressed as a percentage of the total initial protein radioactivity of the cell samples.

Atomic Absorption Spectrophotometry of Intracellular Iron—The total amount of iron in cultured hepatocytes was analyzed using a Polarized Zeeman atomic absorption spectrophotometer Z 8270 (Hitachi, Tokyo, Japan) equipped with an iron lamp (248.3 nm). Hepatocyte proteins were lysed in 500 μl of distilled water (Milli Q, Millipore), diluted 20 times in distilled water, and analyzed in triplicate. Distilled water was used as a blank.

Analysis of Desferrioxamine-available Iron—The free iron pool was determined as the amount of DFX-available iron in a cell homogenate. Cultures (6 × 10⁶ cells) were washed twice in PBS and frozen three times at -18 °C for 15 min. The cells were collected and homogenized in 1 ml of 0.1 M Tris-HCl buffer (pH 7.4). The homogenate was then incubated with 2 mM DFX for 60 min at 37 °C as described by Gower et al. (26). DFX and ferrioxamine (FX) were extracted from the incubation mixture using Sep-Pak C₁₈ cartridges (Millipore) in 2 ml of methanol. A cell-free sample was prepared in the same way and used as a blank. Analysis was performed on a Kromasil 100–5C18 HPLC column (240 × 4.6 mm; Hitachi, Tokyo, Japan) equipped with an iron lamp (248.3 nm). The amount of iron in each sample was calculated as the FDX/DFX ratio from a standard curve (26).

Measurement of Cellular Ferritin by Enzyme-linked Immunosorbent Assay—Hepatocytes grown in 22-mm wells (73,000 cells/cm²) were assayed for ferritin content using a double antibody sandwich enzyme-linked immunosorbent assay with 3,3',5,5'-tetramethylbenzidine as peroxidase substrate. The absorbance of the reaction product was measured at 450 nm using an Anthos HT automated plate reader (Laboratory Design AB, Lidingo, Sweden).

Analysis of the Size of the Intracellular Acidic Compartment Using Acriflavine Orange—Cells, cultured on coverslips (45,000 cells/cm²), were stained with the lysosomotropic weak base, acridine orange (AO) (5 μg/ml in Williams complete medium), for 15 min at 37 °C and then washed in PBS. The coverslip was inverted, placed over a glass well-slide filled with PBS, and the red AO-induced fluorescence intensity was measured in an MPV III microscope photometer using a BG 12 blue activating filter and a 630-nm barrier filter as described previously (29). The fluorescence of 100 cells, randomly selected on each of four coverslips from different cell preparations, was measured.

Measurement of Intralysosomal pH—Cells, cultured on 10 × 40-mm coverslips (73,000 cells/cm²), were allowed to endocytose 0.9 μg/ml fluorescein isothiocyanate-dextran in complete Williams medium for 4 h before they were nutrient-deprived for 1–4 h as described above. The coverslip was then rinsed in PBS, and the fluorescence was determined in a spectrofluorometer (Shimatsu, Japan) at λem 455 nm and λexc 485 nm (30). The pH values were calculated according to a standard curve.

Electron Microscopy—Cell cultures were exposed to amino acid deprivation for 1–4 h and prepared for TEM as described previously (31). The sections were examined and photographed in a JEOL 2000-EX electron microscope (Tokyo, Japan) at 100 kV.

Exposure to Hydrogen Peroxide—Cell cultures were exposed to 50–500 μM hydrogen peroxide in 1.5 ml of PBS at 37 °C for 30 min. The cultures were then washed three times with PBS and returned to normal culture conditions in Williams complete medium, and the viability was tested by the delayed trypan blue exclusion test after 16 h (23).

Statistical Methods—Cell culture experiments were generally repeated four to five times using hepatocytes isolated from different rats. All values are given as arithmetic means ± S.E. The levels of significance were tested with Student’s two-tailed t test for matched pairs.

RESULTS

Effect of Nutrient Deprivation on Cultured Hepatocytes—Initially, the hepatocyte cultures were characterized as to their energy level, glutathione concentration, protein turnover rate, and iron availability. Amino acid- and serum deprivation for 4 h led to a decrease in the intracellular concentration of reduced glutathione of about 35% from the initial value (Fig. 1A). The control cells, incubated in Williams complete medium, showed, on the other hand, a 17% increase in GSH level during the analysis period. The addition of 40 μM ascorbic acid did not affect the glutathione concentration. The ATP level increased slightly in nutrient-deprived cells (Fig. 1B), while control cultures showed no significant changes during the 4-h analysis period. In addition, ascorbic acid had no effect on the energy status.

Table I shows that nutrient deprivation increased the protein turnover by approximately 15%-units as compared with
controls. In agreement with earlier reports protein turnover was not affected by ascorbic acid (16, 20) (results not shown).

Determination of the intracellular ferritin content using enzyme-linked immunosorbent assay analysis showed that ascorbic acid-treated cells contained 14% more ferritin than controls ($p$, 0.05). As shown in Table II the total iron content, as measured by atomic absorption spectroscopy, was not changed significantly during deprivation. However, the DFX-available pool of iron increased 2.5-fold in nutrient-deprived hepatocytes.

If, on the other hand, the cultures were incubated in the presence of 40 $\mu$M ascorbic acid, the DFX-available iron pool was decreased by 48 and 55% in control and amino acid-starved cells, respectively (Table II).

### Table I

| Protein turnover |       |
|------------------|-------|
|                  | 1 h   | 2 h   | 3 h   | 4 h   |
| Control cells    | 22.5 ± 1.4 | 23.3 ± 4.1 | 31.4 ± 2.6 | 34.3 ± 5.4 |
| Nutrient-deprived cells | 31.7 ± 4.6 | 36.1 ± 4.7 | 48.9 ± 5.5 | 53.9 ± 8.4 |

* $p$ ≤ 5%.

** $p$ ≤ 1%.

### Table II

| Iron content |       |       |
|--------------|-------|-------|
|               | Control | Control + ascorbic acid | Nutrient deprivation | Nutrient deprivation + ascorbic acid |
| Total iron   | 42.4 ± 1.0 | ND | 41.6 ± 2.3 | ND |
| DFX-available iron | 1.14 ± 0.16 | 0.59 ± 0.20 | 2.81 ± 0.43 | 1.26 ± 0.10 |

* Marks values significantly different from control, $p ≤ 0.05$.

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**Fig. 2. TEM micrographs showing.** A, control hepatocyte; B, hepatocyte after nutrient deprivation for 1 h. The following structures are marked; nucleus (N), peroxisome (P), mitochondria (M), lysosome (L), autophagic vacuole (A). The Bar is 1 $\mu$m.

**Fig. 3. Determination of the size of the acidic compartment of nutrient-deprived hepatocytes and controls.** Cells were exposed to the lysosomotropic weak acid acridine orange (AO) and the red fluorescence of 100 cells, reflecting accumulation of AO in the acidic compartment, was measured by computer-assisted microfluorometry using an MPV-III microscope. Values are means ± S.E., $n = 4$. * $p$ ≤ 5%; ** $p$ ≤ 2%.

**Autophagocytosis during Nutrient Deprivation**—TEM analysis showed that nutrient deprivation increased autophagy in cultured hepatocytes, since the number of autophagocytic vacuoles increased with time. Fig. 2 shows TEM micrographs of hepatocytes, nutrient-deprived for 1 h, and the corresponding control kept at ordinary culture conditions. Autophagocytosis was also studied by determining the volume of the intracellular acidic compartment, using the lysosomotropic base AO as a marker. AO accumulates in the acidic compartments of the cell where the dye becomes charged and fluoresces at high concentration with a bright red color (29). A significant increase in size of the acidic vacuole was detected after 30 min of nutrient deprivation (Fig. 3). The lysosomal pH was followed during the entire time period, to make sure that the increase in red fluorescence really was due to an actual change in size of the compartment and not to changes in the lysosomal pH during nutrient deprivation causing increased amount of AO to accumulate. The pH was estimated to be 4.68 ± 0.14, which is in agreement with earlier studies (4.70 ± 0.05; see Ref. 32). Furthermore, there was no difference between control and nutrient-deprived cells, and the pH was stable during the 4-h experimental period.

**Hydrogen Peroxide Toxicity**—The susceptibility of hepatocytes to hydrogen peroxide exposure increased with increasing...
time of amino acid and serum deprivation (Fig. 4A). Furthermore, Fig. 4B shows the viability of nutrient-deprived and control hepatocytes after exposure to increasing concentrations of H₂O₂ for 30 min. The LD₅₀ (lethal dose causing 50% cell death) for nutrient-deprived cells was 80 μM, whereas controls showed an LD₅₀ of 255 μM H₂O₂. Incubation with 40 μM ascorbic acid before hydrogen peroxide exposure protected both nutrient-deprived and control cultures against hydrogen peroxide-induced cell death (Fig. 4). In the presence of ascorbic acid, the corresponding LD₅₀ was estimated to 140 and 450 μM in nutrient-deprived and control cells, respectively.

To establish the importance of amount and redox status of lysosomal iron in hepatocyte cultures, the cells were nutrient-deprived for 4 h in PBS containing 1 mM desferrioxamine or 0.25 mM FeCl₃ before exposure to hydrogen peroxide. Desferrioxamine pretreatment protected completely against hydrogen peroxide, as shown in Fig. 5. On the other hand, hepatocytes exposed to 0.25 mM iron(III) chloride showed an augmented sensitivity to hydrogen peroxide resulting in a LD₅₀ of 50 μM (Fig. 5).

To mimic the reduction in the amount of intracellular reduced glutathione that was seen in hepatocytes after nutrient deprivation, control cultures were pretreated with 25 μM DEM for 15 min. This treatment decreased the GSH concentration to 10.6 nmol/mg protein, which was comparable with what was found in hepatocytes nutrient deprived for 4 h (compare Fig. 1A). Hydrogen peroxide was not significantly more toxic to DEM-treated cells than to controls, whereas DEM-treated cells showed significantly higher viability compared with nutrient-deprived cells at hydrogen peroxide concentrations between 50 and 100 μM (Fig. 6). DEM pretreatment did not affect the intracellular ATP concentration (results not shown).

**DISCUSSION**

The autophagocytotic activity of hepatocytes was increased in a pronounced way by amino acid and serum deprivation, as demonstrated by transmission electron microscopy and AO uptake. Furthermore, there was an increased turnover of cellular proteins and the DFX-available pool of iron was increased 2.5-fold. Even if amino acid deprivation is probably not a physiological condition, it was here used as a way to induce general autophagocytic degradation. In the acidic autophagolysosomes, protein-bound iron is released and chelated in various low molecular weight chelates where the iron may be catalytically active. The ATP level was slightly increased during the deprivation period, which indicates that the mitochondrial
function was maintained, a prerequisite for the autophagic process (33). A constant energy level would also keep the cyto-
oplasm stable, which means that accumulation of acidic products would not cause the release of iron from cytosolic ferritin (8, 34). However, the intracellular level of GSH was decreased during deprivation, but since the energy level was sustained, this might be due to a lack of cysteine.

There was no change in the total iron content of the cells during the nutrient deprivation, and, thus, a redistribution of intracellular iron in favor of a more available pool has obviously occurred. The low molecular weight iron pool is estimated to be 0.2–3% of the total iron content (35, 36). In this study we found that 2.7% of the total iron content of control cells was available to DFX. However, it is not likely that all detected DFX-available iron is drawn from a pool of iron in the form of low molecular weight chelates. Gower et al. (26) have shown that DFX is also able to remove iron from ferritin to some extent. DFX-available iron is drawn from a pool of iron in the form of low molecular weight chelates. Gower et al. (26) have shown that DFX is also able to remove iron from ferritin to some extent. DFX-available iron is drawn from a pool of iron in the form of low molecular weight chelates.

The cellular toxicity of hydrogen peroxide has been explained as a cascade of biological oxidations resulting in a rapid modification of cytoplasmic constituents, depletion of intracellular GSH and ATP, decrease in NAD+ level, increase in free cyto-
solic Ca2+, and initiation of lipid peroxidation (9–13, 37). Most importantly, hydrogen peroxide is a potential source of one of the most dangerous radical known, the hydroxyl radical, through the Fenton reaction. This study, and several others, have lately shown that increase of cellular iron content ob-
viously occurs. The low molecular weight iron pool is estimated to be 0.2–3% of the total iron content (35, 36). In this study we found that 2.7% of the total iron content of control cells was available to DFX. However, it is not likely that all detected DFX-available iron is drawn from a pool of iron in the form of low molecular weight chelates.

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Nutrient Deprivation of Cultured Rat Hepatocytes Increases the Desferrioxamine-available Iron Pool and Augments the Sensitivity to Hydrogen Peroxide

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