Relation of Mevalonate Synthesis to Mitochondrial Ubiquinone Content and Respiratory Function in Cultured Neuroblastoma Cells

(Received for publication, April 15, 1985)

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The consequence of blocking the de novo synthesis of ubiquinone (coenzyme Q) on mitochondrial ubiquinone content and respiratory function was studied in cultured C1300 (Neuro 2A) murine neuroblastoma cells. Mevinolin, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, was used to suppress the synthesis of mevalonate, an essential precursor for the isoprenoid side chain of ubiquinone. At a concentration of 25 μM, mevinolin completely inhibited the incorporation of [3H]acetate into ubiquinone, isolated from cell extracts by two-dimensional thin-layer chromatography. Similar results were obtained when [14C]tyrosine was used as a precursor for the ubiquinone ring. Through the use of reverse-phase thin-layer chromatography, it was established that the principal product of the ubiquinone pathway in murine neuroblastoma cells was ubiquinone-9. Inhibition of ubiquinone synthesis for 24 h in cells cultured in the presence of 10% fetal calf serum (which contains 0.14 nmol of ubiquinone/ml of serum) resulted in a 40–57% decline in the concentration of ubiquinone in the mitochondria. However, the activities of succinate-cytochrome c reductase and succinate dehydrogenase in whole-cell homogenates or mitochondria were not inhibited. The rate and uncoupled rates of respiration, determined by polarographic measurements of oxygen consumption in homogenates and mitochondria, were elevated slightly in the mevinolin-treated cells. The data demonstrate that, although mevalonate synthesis is important for the maintenance of the intramitochondrial ubiquinone pool in cultured cells, major changes in the ubiquinone content of the mitochondria can occur in intact cells without perturbation of respiratory function. However, the coincidence of decreased mitochondrial ubiquinone concentration and the inhibition of cell cycling previously observed in mevinolin-treated cells (Maltese, W. A. (1984) Biochem. Biophys. Res. Commun. 120, 454–460) suggests that the availability of ubiquinone may play a role in the regulation of mitochondrial and cellular proliferation.

Ubiquinone (coenzyme Q) functions as a mobile carrier of reducing equivalents between the flavin-linked dehydrogenases of complexes I and II and the cytochrome bc1 complex (complex III) of the mitochondrial respiratory chain (1, 2). Ubiquinone contains a 2,3-dimethoxy-5-methyl-1,4-benzoquinone moiety and a polyisoprene side chain that plays an essential role in the interaction of the molecule with the lipids of the mitochondrial membrane (3–5). The isoprenoid chain of ubiquinone is derived from mevalonate, which also serves as a precursor for sterols and dolichols in eucaryotic cells (for reviews see Refs. 6 and 7). The formation of mevalonate, catalyzed by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, is regarded as the major regulatory step for de novo cholesterol biosynthesis (8–10). It is now recognized that factors which influence the activity of HMG-CoA reductase and the rate of sterol synthesis in cultured cells (e.g. low-density lipoprotein cholesterol, oxygenated sterols, competitive inhibitors of the reductase) also produce major changes in the rate of ubiquinone synthesis (11–13). However, since animals can derive ubiquinone from dietary sources as well as from de novo synthesis, the implications of changes in HMG-CoA reductase activity for the regulation of mitochondrial ubiquinone content and respiratory function in vivo remain unclear.

Proliferating cells undergo an approximate doubling of mitochondrial mass during the cell cycle (14–17), suggesting that various components of the electron transport system must be available for biogenesis of new functional mitochondrial inner membrane. Although ubiquinone is present in stoichiometric excess of the cytochromes and other proteins of the respiratory chain (18–20), recent studies with isolated mitochondria have shown that the activities of NADH-, succinate-, and ubiquinone-cytochrome c reductase are sensitive to experimental modifications of the ubiquinone content of the mitochondrial membrane (21). Thus, an important unanswered question is whether fluctuations in the synthesis of isoprenoid precursors (e.g. mevalonate) in intact cells can cause changes in the intramitochondrial ubiquinone concentration of a magnitude sufficient to alter the functional properties of the electron transport system. In the present study we used mevinolin, a potent competitive inhibitor of HMG-CoA reductase (22), to address this question in cultured neuroblastoma cells. The data show that, although the ubiquinone content of the mitochondria decreases markedly in response to inhibition of mevalonate synthesis, respiratory function is not impaired.

EXPERIMENTAL PROCEDURES

Materials—[3H]Acetic acid, sodium salt (100 mCi/mmol), and L-[1-14C]tyrosine (625 mCi/mmol) were purchased from New Eng-

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* This work was supported by United States Public Health Service Grants RO1 CA 34569 (to W. A. M.) and RO1 NS 14936 and RO1 HD 16836 (to J. R. A.) and by a grant from the Marion and Jasper Whiting Foundation. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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¶ The abbreviations used are: HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; DCIP, 2,5-dichloroindophenol.

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obtained from Amersham Corp. Thin-layer chromatography plates (Brinkmann Instruments), tissue culture medium (Gibco Laboratories, Grand Island, NY), fetal calf serum (Kansas City Biological Co., Lenexa, KA), and plastic tissue culture flasks (Falcon, Oxnard, CA) were purchased from the designated sources. Lipid and ubiquinone standards and other biochemicals were obtained from Sigma. All organic solvents were A.C.S. Spectranalyzed Grade from Fisher. Mevinolin was a gift from Dr. Alfred W. Alberts of the Merck Sharp and Dohme Institute for Therapeutic Research, Rahway, NJ. The lactone form of mevinolin was converted to the sodium salt as described by Kita et al. (23) prior to addition of the compound to the culture medium.

Cell Culture—The C1300 murine neuroblastoma (Neuro 2A) cell line was obtained from the American Type Culture Collection, Rockville, MD. For all experiments, cells were grown in monolayer culture at 37 °C in Dulbecco's modified Eagle's medium without antibiotics, supplemented with 10% (v/v) fetal calf serum. The concentration of ubiquinone in the fetal calf serum was determined to be 0.14 nmol/ml (see below). The culture medium contained 2.2 g/liter sodium bicarbonate and was equilibrated with a humidified atmosphere of 5% CO2 in air. Periodic tests for the presence of Mycoplasma, performed with Mycoptrim broth-agar culture kits (Hansa Professional, Biox, Berchem, Belgium) were negative. Cells were incubated for 24 h at 37 °C under full irradiation. Cultures were subcultivated by exposing the monolayers to 0.25% trypsin in Dulbecco's phosphate-buffered saline, pH 7.5, for 10 min. Trypsin was inactivated by suspending the cells in medium with 10% fetal calf serum, and cell number was routinely determined with a Coulter counter (Model ZB).

Labeling and Extraction of Cellular Lipids—To measure the incorporation of labeled precursors into ubiquinone and other lipids, neuroblastoma cells were grown in 175-cm2 flasks for 24 h. The medium was then replaced with 20 ml of fresh medium containing [3H]acetyl, [3H]acetate, or [14C]acetate, and the cultures were incubated at 37 °C. The concentrations of labeled precursors and the durations of the incubations varied in different experiments and are described in the appropriate figures or table legends. After removing the radioactive medium, the cells were scraped into ice-cold Dulbecco's phosphate-buffered saline, pH 7.5, and pelleted by centrifugation at 500 x g for 5 min. Cell pellets were washed three times with cold buffered saline solution and stored at −80 °C in tubes flushed with nitrogen. Prior to extraction of lipids the cell pellets were suspended in 1.6 ml of 0.15 M NaCl, and duplicate 50-μl aliquots were removed for determination of protein by a microbiuret method (24). The following lipid standards, dissolved in 100 μl of chloroform, were added to the suspending cell suspension: cholesterol (60 μg), lanosterol (50 μg), dolichol (15 μg), ubiquinone-10 (coenzyme Q10) (30 μg), squaleone (10 μg), cholesteryl oleate (75 μg), triolein (75 μg), 1,3-diol (37 μg), 1,2-diol (12 μg), monolyle (50 μg), oleic acid (80 μg), and phosphatidylcholine (20 μg each). In some experiments, the lipids were oxidized on the cell pellets by ubiquinone-7 (catalytic amounts). Lipids were extracted from the cell suspension with chloroform/methanol (2:1, v/v), using a modification of the method of Folch et al. (25, 26). The lipids in the lower phase were condensed by evaporating the chloroform under a stream of nitrogen, and thin-layer chromatography was performed as described below.

Isolation of Ubiquinone by Thin-layer Chromatography—Thin-layer plates, precoated with Silica Gel G-25 (0.25-mm thickness, 20 × 20 cm), were activated in an oven at 100 °C for 30 min. Cellular lipids with the added lipid standards were dissolved in chloroform and spotted at the origin, 1.5 cm from the bottom of the plate and 2 cm from the left edge. Evaporation of the solvent was carried out under a stream of nitrogen. Chromatography in the first dimension was carried out at room temperature in a solvent system of hexane/diethyl ether/glacial acetic acid (70:30:1.5, v/v/v), and the plates were allowed to dry in air for 1 min. Benzene was used to develop the chromatograms in the second dimension, and the plates were dried under a stream of nitrogen. Chromatography in the first dimension was carried out at room temperature in a solvent system of hexane/diethyl ether/glacial acetic acid (70:30:1.5, v/v/v), and the plates were allowed to dry in air for 1 min. Benzene was used to develop the chromatograms in the second dimension, and the plates were dried under a stream of nitrogen. Chromatograms containing the gel, along with the attached pipette tips, were transferred into scintillation vials containing 10 ml of Econofluor (New England Nuclear). Vials containing collection tubes and gel from the lipid-free margin of the thin-layer plate served as blanks. Samples were counted in a Packard Tri-Carb liquid scintillation spectrometer (model 2055), and the counting efficiency was determined by the external standards channel ratio method.

To further characterize the labeled cellular material co-migrating with authentic ubiquinone on the two-dimensional chromatogram, the ubiquinone spot was visualized under short-wave UV light and eluted with 0.5 ml of chloroform. This elution was then rechromatographed in two different systems. Conventional single dimension chromatography was performed on silica Gel G-25 plates which were activated at 100 °C for 30 min and developed with methylene chloride/ethyl acetate (97:3, v/v). Reverse-phase chromatography was performed on Silica Gel G-25 plates that had been dipped in chloroform and ether and dried for 30 min. The solvent system consisted of acetone/paraffin-saturated water (85:15, v/v) (28). The thin-layer plates were subjected to autoradiography by exposing them to Ultrofilm (LKB Instruments, Inc., Paramus, NJ) for 7 days at −80 °C. Following autoradiography, the position of the ubiquinone standards was visualized under short-wave UV light, and the gel was scraped and counted in a liquid scintillation spectrometer, as described above.

Preparation of Homogenates and Mitochondria for Ubiquinone Extraction, Respiration, and Enzyme Assays—Cells that had been incubated with [14C]acetate were washed twice with ice-cold buffered saline and pelleted by centrifugation at 500 × g for 10 min at 4 °C. The supernatant solution was removed, and centrifuged at 12,000 × g for 20 min to obtain a crude mitochondrial pellet, which was used for the assays described below. Respiration was always assayed immediately, whereas succinate dehydrogenase, succinate-cytochrome c reductase, and ubiquinone were measured in preparations that were frozen at −80 °C.

Enzyme Assays—Activity of succinate dehydrogenase was measured by a modification of the phenazine methosulfate assay described by Singer (30). The reaction mixture contained 50 mM potassium phosphate, pH 7.4, 2 mM sodium cyanide, 25 mM sodium succinate, 2 mM phenazine methosulfate, and 0.1 mM DCIP in a final volume of 1 ml. The final protein concentrations in the assay were 35–45 μg/ml for homogenates and 25–40 μg/ml for mitochondrial preparations. All protein samples were treated with Triton X-100 (0.01% final concentration) before being added to the assay medium. After a 1-min preincubation, reactions were started by addition of phenazine methosulfate and DCIP, and the linear decrease in absorbance at 600 nm was recorded. The reduction of cytochrome c in the reaction mixture with succinate for 1 min to be certain that the enzymes were present. Enzyme activities were calculated as the slope of the linear increase in absorbance of cytochrome c. Succinate-cytochrome c reductase activity was assayed by measuring the linear increase in absorbance of cytochrome c at 550 nm in the presence of succinate. The reaction mixture contained 50 mM potassium phosphate, pH 7.4, 2 mM sodium cyanide, 20 mM sodium succinate, and 0.1% (w/v) oxidized cytochrome c in a total volume of 1 ml. Protein concentrations in the reaction mixture were 30–40 μg/ml for homogenates and 25–40 μg/ml for mitochondria. The reaction was started by addition of ubiquinone-7 (catalytic amounts). A final concentration of 0.01% was added to all protein samples prior to assay. As in the succinate dehydrogenase assay, protein samples to be assayed for succinate-cytochrome c reductase were preincubated in the reaction mixture with succinate for 1 min to be certain that the enzyme complexes were fully activated prior to initiating the reaction. Enzyme activities were calculated as the slope of the linear increase in absorbance of cytochrome c. NADH-cytochrome c reductase activity was assayed in the presence of 1 nmol of DCIP oxidized per min at 30 °C, using a millimolar extinction coefficient of 19.1 for DCIP.

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concentration of ubiquinone was determined with an Aminco DW-2a dual wavelength spectrophotometer by measuring the absorbance at 280–289 nm of oxidized versus borohydride-reduced samples, using an extinction coefficient of 8.8 mm$^{-1}$cm$^{-1}$. The same procedure was used to assay ubiquinone in fetal calf serum.

**Respiratory Activity**—Oxygen utilization was measured polarographically in freshly prepared homogenates and mitochondria using a Clark-type O$$_2$$ electrode at 30 °C, essentially as described previously (32). The assay medium contained 225 mM sucrose, 10 mM Tris-HCl, 10 mM potassium phosphate, 10 mM KCl, 5 mM MgCl$_2$, 1 mM EDTA, all at pH 7.4. Aliquots of homogenate (1.0–1.5 mg of protein) or mitochondria (0.3–0.5 mg of protein) were added, followed by 1 µM rotenone and 10 mM succinate. 150 µM ADP was added next to elicit coupled respiration (state 3). After the linear rate was recorded, 0.25 µM carbonyl cyanide m-chlorophenylhydrazone was added to obtain the uncoupled respiratory rate.

**RESULTS**

**Effects of Mevinolin on Incorporation of Labeled Precursors into Ubiquinone**—To study the effects of mevinolin on ubiquinone synthesis in cultured neuroblastoma cells, we used [3H]mevalonate or [14C]acetate as precursors for the isoprenoid chain and [14C]tyrosine as a precursor for the quinone ring of the molecule. Acetate was preferred over mevalonate as an isoprenoid precursor because competitive inhibitors of HMG-CoA reductase apparently decrease the size of the intracellular mevalonate pool, thereby causing an increase in the labeling of ubiquinone with [3H]mevalonate which probably reflects an increase in the specific radioactivity of the intracellular mevalonate pool, rather than a true increase in the rate of ubiquinone synthesis (11–13). However, because acetate is incorporated into non-isoprenoid lipids, it was necessary to use a two-dimensional thin-layer chromatography system to ensure complete separation of ubiquinone from other lipids (Fig. 1a). When cells were incubated with [14C]acetate, the labeled material that co-migrated with authentic ubiquinone on the two-dimensional chromatogram yielded a single band of radioactivity when eluted and rechromatographed on conventional silica gel plates using a third solvent system (Fig. 1b). There was no indication of contamination of ubiquinone with dolichol or free fatty acids, the lipids nearest to ubiquinone on the two-dimensional chromatogram. However, since ubiquinone-10 and ubiquinone-9 migrate together on conventional thin-layer plates, we also subjected the [14C]acetate-labeled material to reverse-phase thin-layer chromatography in a system capable of separating ubiquinone species according to the length of the isoprenoid chain (Fig. 1c). The results indicated that approximately 90% of the radioactive product synthesized by the murine neuroblastoma cells was ubiquinone-9. In this respect the mouse neuroblastoma cells are similar to rat tissues (33–36) and differ from human fibroblasts, where ubiquinone-10 predominates (11). Chromatographic analysis using ubiquinone-6 and ubiquinone-7 as carriers in the two-dimensional and reverse-phase systems showed no detectable incorporation of labeled acetate into the short-chain ubiquinone species (data not shown). In the reverse-phase system there was no evidence of rapidly migrating isoprenoids, such as squalene dioxides, which have been reported to co-migrate with ubiquinone in some conventional chromatography systems (28).

To assess the effects of mevinolin on de novo synthesis of ubiquinone in neuroblastoma cells, we measured the incorporation of [3H]acetate into ubiquinone in cells that were exposed to various concentrations of the reductase inhibitor for 24 h (Fig. 2). To control for possible nonspecific effects of mevinolin on acetate uptake or the size of the intracellular acetyl-CoA pool, we also measured the incorporation of [3H]acetate into fatty acids in the same cultures (Fig. 2). Maximum inhibition of ubiquinone synthesis was observed at mevinolin concentrations above 10 µM. The suppression of ubiquinone synthesis by 25 µM mevinolin was apparent by 1 h after addition of the inhibitor, and was demonstrable with [14C]tyrosine as well as with [3H]acetate (Table 1).

**Effects of Blocking Mevalonate Synthesis on Mitochondrial Ubiquinone Content**—When ubiquinone was measured in mitochondrial extracts from cells that had been exposed to 25 µM mevinolin for 24 h, we found that the inhibition of
ubiquinone synthesis was accompanied by a 40% decrease in the concentration of ubiquinone/mg of mitochondrial protein (Table II). To compensate for variations in mitochondrial enrichment in this experiment, the ubiquinone concentrations also were expressed on the basis of succinate dehydrogenase recovered in the 12,000 × g pellets. The activity of succinate dehydrogenase was not affected by mevinolin (see Table III). The ratio of ubiquinone to succinate dehydrogenase activity in the mitochondria from the mevinolin-treated cultures was decreased by 57% compared to the control mitochondrial preparations (Table II).

**Effects of Mevinolin on Mitochondrial Enzyme Activities**—In a separate experiment designed to evaluate the effects of blocking ubiquinone synthesis on the integrity of the respiratory complexes of the inner mitochondrial membrane, we performed enzymatic determinations of electron transport activity between succinate and cytochrome c (i.e. succinate-cytochrome c reductase) in cultures treated with mevinolin for 24 h. In order to assess the relative numbers of mitochondria in the whole-cell homogenates and compare the purity of the mitochondrial fractions derived from the control and mevinolin-treated cultures, we also measured the activity of succinate dehydrogenase, using an assay in which an artificial electron acceptor (phenazine methosulfate) is substituted for ubiquinone. Mevinolin had no effect on the specific activity of succinate dehydrogenase in the whole-cell homogenates. Moreover, the approximate 3-fold enrichment of this enzyme in the corresponding cell homogenate. Mevinolin did not significantly affect the activity of succinate-cytochrome c reductase in the whole-cell homogenates or the mitochondria-enriched fractions (Table III).

**Effects of Mevinolin on Respiratory Activity**—Polarographic measurements of oxygen consumption in freshly isolated intact mitochondria were used as an alternate approach to compare respiratory activity in control cultures and cultures in which ubiquinone synthesis had been suppressed for 24 h with mevinolin. We again assayed both whole-cell homogenates and isolated mitochondria in order to distinguish between changes in oxygen consumption that might be due to
Neuroblastoma cultures were seeded in 175-cm² flasks and treated with mevinolin as described in the legend to Table III. Polarographic measurements of oxygen consumption were performed on homogenates and 12,000 × g mitochondrial pellets as described under “Experimental Procedures.” For each determination, four cultures were pooled. Each value is the mean ± S.E. of three separate determinations performed on groups of parallel cultures.

The increased rate of oxygen consumption (uncoupled) in the cultures treated with mevinolin was significant at p = 0.005 for homogenates and p = 0.05 for mitochondria.

### TABLE IV

| Sample          | Rate of oxygen consumption | Acceptor control ratio | Rate of oxygen consumption |
|-----------------|----------------------------|------------------------|----------------------------|
|                 | State 3                   | Uncoupled              | State 3                   | Uncoupled              |
| Homogenates     |                           |                        |                           |                        |
| Controls        | 19.1 ± 1.8                | 20.7 ± 0.7             | 389 ± 17                  | 422 ± 14               |
| + Mevinolin     | 26.5 ± 0.6                | 29.4 ± 0.9             | 528 ± 13                  | 586 ± 20               |
| Mitochondria    |                           |                        |                           |                        |
| Controls        | 55.1 ± 2.7                | 62.1 ± 5.2             | 1.8 ± 0.1                 |                          |
| + Mevinolin     | 65.0 ± 1.2                | 74.5 ± 2.8             | 2.4 ± 0.7                 |                          |

### DISCUSSION

The importance of mevalonate as a precursor for the synthesis of ubiquinone has been documented in various mammalian tissues, including liver (33–35), kidney (33), heart (33), intestine (33), skin fibroblasts (11, 12), and glioma cells (36, 37). In this study we have shown that inhibition of mevalonate synthesis for 24 h results in a marked decline in the concentration of ubiquinone in the mitochondria of cultured neuroblastoma cells. The data indicate that, despite the availability of some exogenous ubiquinone in the fetal calf serum used to supplement the culture medium, continuous synthesis of mevalonate is required for the maintenance of a constant intramitochondrial pool of ubiquinone. In considering the relevance of this finding to tissues in vivo, it should be noted that the concentration of ubiquinone that we detected in fetal calf serum (0.14 nmol/ml) was only 10–20% of that reported for human serum (38, 39). Moreover, the fetal calf serum was diluted 1:10 in the tissue culture medium. Therefore, the observed relationship between mevalonate synthesis and mitochondrial ubiquinone content may be more relevant to tissues with restricted access to serum low-density lipoprotein ubiquinone (e.g., neuronal and glial elements of the central nervous system) than to tissues such as the liver or intestine.

Early studies using selective extraction of mitochondrial ubiquinone with organic solvents, followed by partial or complete restoration of the ubiquinone, established the essential role of ubiquinone in the transfer of electrons from the succinate dehydrogenase complex to the cytochromes of complex III (40–43). Therefore, our finding that it was possible to decrease the intramitochondrial concentration of ubiquinone by as much as 46–57% in intact cells without adversely affecting the activity of succinate-cytochrome c reductase or the rate of coupled oxidative phosphorylation was particularly striking. Several possible interpretations of this observation can be proposed in light of current models for ubiquinone function. For example, Yu and Yu (44) have suggested that the transfer of electrons between complexes II and III requires the specific binding of ubiquinone to proteins in complex II. If this is true, then it is possible that only a fraction of the total ubiquinone pool is required to saturate the protein-binding sites. Alternatively, experiments by Klingenberg and co-workers (45, 46) have suggested that submitochondrial particles isolated from beef heart contain two distinct populations of ubiquinone molecules; a large redox-active population (80–90%) which behaves kinetically as a homogeneous pool and a small population (10–20%) that does not undergo reduction. If the ratio of inactive to active ubiquinone in neuroblastoma mitochondria is substantially higher than in beef heart mitochondria, this might explain why respiratory function remains intact despite the large decrease in ubiquinone concentration produced by mevinolin.

We have shown previously that exposure of cultured neuroblastoma cells to mevinolin for 24 h leads to cessation of cell proliferation and increased expression of differentiated properties (47). Arrest of cell proliferation also has been observed in a variety of non-neuronal cell lines treated with competitive inhibitors of HMG-CoA reductase (48–52). The present data demonstrate that the arrest of cell proliferation is not mediated by a disruption of mitochondrial respiratory function. Nevertheless, it remains possible that inhibition of ubiquinone prevents the completion of the cell cycle by hindering mitochondrial biogenesis. For instance, the activity of HMG-CoA reductase has been reported to reach a peak just prior to the entrance of synchronized cells into the S-phase of the cell cycle (50). Thus, one might speculate that rapidly proliferating cells may synthesize an excess of ubiquinone during part of the cell cycle to allow for the eventual doubling of the number of mitochondria in preparation for cell division (14–17). When ubiquinone synthesis is inhibited by more than 90%, as it is at high concentrations of mevinolin, the availability of ubiquinone might become a limiting factor for the assembly of the inner mitochondrial membrane, i.e. mitochondrial biogenesis might be arrested before a significant number of defective mitochondria can accumulate. In this way the cellular energetics may be preserved at the expense of continued mitochondrial proliferation and cell growth, and the respiratory activity of the available mitochondria would appear normal when assayed by polarographic or enzymatic methods. Consistent with this hypothesis, our data showed...
that neither the relative numbers of mitochondria per cell (i.e., specific activity of mitochondrial enzymes/μg of DNA in homogenates) nor the respiratory activity of the mitochondria themselves was decreased by mevinolin. Mevinolin inhibits cholesterol synthesis as well as ubiquinone synthesis. Therefore, our finding of small but consistent increases in the coupled and uncoupled respiratory rates in intact mitochondria from mevinolin-treated cultures (Table IV) was intriguing in light of recent reports that changes in G., Hensens,

IV) was intriguing in light of recent reports that changes in G., Hensens,

increased oxygen consumption rates observed in intact mitochondrial membranes from mevinolin (Table IV) were due to enhanced succinate transport.

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Mevalonate Synthesis, Ubiquinone, and Respiratory Function

Acknowledgments—We are grateful to Dr. Alfred W. Alberts for providing mevinolin. We also thank Dr. Darryl C. De Vivo for helpful comments and Alice H. Marti for typing the manuscript.