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Myopathy Induced by HMG–CoA Reductase Inhibitors in Rabbits: A Pathological, Electrophysiological, and Biochemical Study

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A combination of electrophysiological, pathological, and biochemical studies were performed in myopathy induced by 3-hydroxy-3-methylglutaryl–coenzyme A (HMG–CoA) reductase inhibitors. Simvastatin (a lipophilic inhibitor) or pravastatin (a hydrophilic inhibitor) were administered by gavage to rabbits. In Group I (simvastatin-treated group, 50 mg/kg/day for 4 weeks), four rabbits showed muscle necrosis and high serum creatine kinase (CK) levels, and all six rabbits showed electrical myotonia. In Group II (pravastatin-treated group, 100 mg/kg/day for 4 weeks), no rabbit showed either condition. In Group III (pravastatin-treated group, 200 mg/kg/day for 3 weeks plus 300 mg/kg/day for 3 weeks), one rabbit showed muscle necrosis and high serum CK level and two rabbits showed electrical myotonia. The pathological findings were muscle fiber necrosis and degeneration with increased acid phosphatase activity by light microscopy, autophagic vacuoles and mitochondrial swelling, and disruption and hypercontraction of myofibrils by electron microscopy. Ubiquinone content decreased in skeletal muscle by 22 to 36% in Group I, by 18 to 52% in Group II, and by 49 to 72% in Group III. However, mitochondrial enzyme activities of respiratory chain were normal in all groups. These results indicate that myopathy was not induced by a secondary dysfunction of mitochondrial respiration due to low ubiquinone levels. © 1998 Academic Press

Key Words: **HMG–CoA reductase inhibitor; rhabdomyolysis; pathology; myotonia; ubiquinone; mitochondrial enzyme; respiratory chain.**

Hypercholesterolemia is a major risk factor for atherosclerosis. 3-Hydroxy-3-methylglutaryl (HMG)[2]–CoA reductase (HCR) is a key enzyme in the pathway of cholesterol biosynthesis, catalyzing the formation of mevalonate from HMG–CoA (Goldstein and Brown, 1990). Inhibitors of HCR sharply decrease the serum cholesterol level. There are two forms of HCR inhibitors: a lipophilic form (such as lovastatin or simvastatin) and a hydrophilic form (pravastatin) (Hoeg, 1990). Simvastatin is approximately 200-fold more lipophilic than pravastatin (Serajuddin *et al.,* 1991). Because of its benefit, several HCR inhibitors are being used worldwide (Hoeg, 1990; Hunninghake, 1992; Mantell *et al.,* 1990; Tobert, 1988).

The most important adverse effect of HCR inhibitors is muscle necrosis, manifesting as myalgia, limb weakness, elevation of serum creatine kinase (CK), and myoglobinuria (rhabdomyolysis) (Hunninghake, 1992). Myopathy is a rare occurrence (0.1–0.2% of all patients treated) (Tobert, 1988), though it increases with simultaneous administration of immunosuppressants (Corpier *et al.,* 1988; Norman *et al.,* 1988; East *et al.,* 1988); hypolipidemic agents, e.g., gemfibrozil (East *et al.,* 1988; Pierce *et al.,* 1990); and niacin (Norman *et al.,* 1988; Reaven and Witztum, 1988). In cardiac transplant patients, for instance, 30% developed myopathy upon receiving cyclosporine A with HCR inhibitors (Tobert, 1988). Likewise, a severe myopathy has been seen in people treated with lovastatin, simvastatin (Berland *et al.,* 1991), and pravastatin (Schalke *et al.,* 1992).

How myopathy occurs as induced by HCR inhibitors remains unclear. Smith *et al.* (1991) developed an experimental HCR inhibitor-induced myopathy in rats. High dosages of four different HCR inhibitors induced skeletal muscle degeneration, which was thought to be due to impaired muscle energy metabolism. Studies indicate that HCR inhibitors slow the formation of mevalonate, which is a precursor not only of sterols but also of ubiquinone (coenzyme Q). Coenzyme Q is an essential component of the electron transport chain in mitochondria (Goldstein and Brown, 1990). Lovastatin decreases ubiquinone levels in rats (Willis *et al.,* 1990) and in humans (Folkers *et al.,* 1990). Moreover, myoglobinuria or rhabdomyolysis have been seen in patients

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[2] Abbreviations used: ALP, alkaline phosphatase; BUN, blood urea nitrogen; CK, creatine kinase; CMC, carboxymethylcellulose; Cr, creatinine; EDL, extensor digitorum longus; EMG, electromyography; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; HCR, HMG–CoA reductase; HMG–CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; NADH–TR, NADH–tetrazolium reductase; PAS, periodic acid–Schiff; SOL, soleus.

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with mitochondrial myopathy attributed to multiple deletions of mitochondrial DNA (Ohno *et al.,* 1991). There is therefore a suggestion of defects in the mitochondrial energy–transduction system. On the other hand, Waclawik *et al.* (1993) reported an experimental lovastatin-induced myopathy in rats and found that the gastrocnemius muscle (a fast-twitch muscle) was vulnerable (i.e., severe degeneration of membranous organelles with microvacuole formation), while that of the soleus (SOL) muscle (a slow-twitch muscle) was spared. They inferred that the primary cause of the myopathy was not due to interference with mitochondrial energy production.

We have described an experimental myopathy in rabbits induced by simvastatin (Nakahara *et al.*, 1992). In that study, the rabbits exhibited electrical myotonia, muscle necrosis, and high serum levels of sarcoplasmic enzymes. This combination of findings suggested damage to the muscle surface membranes. However, reduction in ubiquinone levels that could potentially alter the mitochondrial respiration have been implicated in the pathogenesis of myopathy. The present study was undertaken to further investigate the mechanism of HCR inhibitor-induced myopathy. First, we compared the myotoxicity of lipophilic simvastatin and hydrophilic pravastatin. Second, we characterized the myopathy both by histochemical and electrophysiologic studies. Finally, biochemical studies were undertaken to determine whether reductions in ubiquinone levels impair the mitochondrial respiratory chain and thereby cause myopathy.

MATERIALS AND METHODS

Animals and drugs. Male New Zealand white rabbits, aged 5 to 6 months and weighing 2.7 to 3.1 kg, were housed individually and raised with commercial rabbit chow (R-stock, Nippon Nosan Kogyo, Kanagawa, Japan). The rabbits were divided into three groups: Group I included six rabbits that received 50 mg/kg simvastatin suspended in 0.5% carboxymethylcellulose (CMC) by gavage once a day for 4 weeks; Group II included eight rabbits that received 100 mg/kg pravastatin once a day for 4 weeks; and Group III included five rabbits that received pravastatin at the dose of 200 mg/kg for 3 weeks and at the dose of 300 mg/kg for the following 3 weeks. In the control group, five rabbits received in a similar manner 0.5% CMC solution, excluding inhibitors. This study was carried out in accordance with Guides for Animal Experimentation, Faculty of Medicine, Kagoshima University.

Measurement of serum lipids, enzymes, and electrolytes. Blood samples were drawn from an auricular vein every 7 days and were obtained through cardiac puncture upon euthanasia. Cholesterol, triglycerides, and phospholipid were measured enzymatically. Serum CK, transaminases (GOT and GPT), alkaline phosphatase (ALP), creatinine (Cr), blood urea nitrogen (BUN), and electrolytes including K^+, Na^+, and Cl^- were conventionally measured through an autoanalyzer.

Electrophysiological examination. Concentric needle electromyography (EMG) was carried out in lumbar paraspinal muscles every 7 days without anesthesia. Insertion activity and motor unit potentials were recorded using a disposable concentric needle (DMC50, Medelec, Surrey, UK) and a Medelec 92B recorder (Medelec).

Morphologic studies of muscle. All rabbits were euthanized under anesthesia upon termination of the final EMG examination. SOL and extensor digitorum longus (EDL) muscles were obtained from both legs. For histochemical studies, the muscle specimens were immediately frozen in isopentane chilled in liquid nitrogen and kept in a liquid nitrogen tank until ready for morphologic study. Serial frozen sections were stained by H & E, modified Gomori-trichrome, periodic acid–Schiff (PAS), oil red O, NADH–TR, and ATPase, according to the methods of Dubowitz and Brooke (1973). Acid phosphatase was stained by the method of Barka and Anderson (1962), and cytochrome c oxidase was treated by the method of Seligman *et al.* (1968). For the electron microscopic study, specimens were fixed in cacodylate-buffered 2% glutaraldehyde solution for 2 h and were postfixed in 1% buffered osmium tetroxide and then embedded in Epon. Semithin sections (1 μm) were stained with 0.2% toluidine blue. Ultrathin sections were cut, counter-stained with uranyl acetate and lead citrate, and examined under an electron microscope.

TABLE 1
Percent Reduction of Serum Lipids in Rabbits

	Group I (simvastatin 50) (n = 6) (%)	Group II (pravastatin 100) (n = 8) (%)	Group III (pravastatin 200/300) (n = 5) (%)
Total cholesterol	−55.4***	−52.8***	−62.5**
Phospholipid	−27.9*	−33.5**	−41.1***
Triglycerides	+12.7	−38.6***	−28.3*

Note. Group I, simvastatin-treated rabbits (50 mg/kg/day for 4 weeks); Group II, pravastatin-treated rabbits (100 mg/kg/day for 4 weeks); Group III, pravastatin-treated rabbits (200 mg/kg/day for 3 weeks + 300 mg/kg/day for 3 weeks).
***$p < 0.005$; **$p < 0.01$; *$p < 0.05$; paired t-test.

Measurement of ubiquinones. After ubiquinols were oxidized to ubiquinones with ferric chloride, ubiquinone content in frozen tissue samples from skeletal muscles and several organs was measured using HPLC by the method of Nobuyoshi *et al.* (1984).

Assays of mitochondrial enzyme activities. Muscles were immediately frozen in liquid nitrogen and stored at −80°C until biochemical analysis. Frozen muscles of SOL and EDL were homogenized in 9 vol of 0.15 M KCl and 0.05 M Tris–HCl (pH 7.5) by motor-driven glass homogenizers (Wheaton type) at 4°C. Mitochondrial enzymes were measured in supernatant fluid after centrifugation at 1000*g* for 15 min. NADH–cytochrome c reductase (Sottocasa *et al.*, 1967), succinate–cytochrome c reductase (Sottocasa *et al.*, 1967), cytochrome c oxidase (Wharton and Tzagoloff, 1967), and citrate synthase (Srere, 1969) were determined by spectrophotometric assays.

RESULTS

Changes of Serum Lipids (Table 1) and CK Levels (Fig. 1)

Serum cholesterol and phospholipid levels decreased significantly in all groups. Triglyceride levels varied among rabbits in each group. Serum CK levels markedly increased (>10-fold) in four of six rabbits of Group I (simvastatin 50-mg-treated group). In this group, CK levels peaked at the 2nd or 3rd week, and then returned to basal levels at the 4th week. In Group II (pravastatin 100-mg-treated group) and Group III (pravastatin 200- to 300-mg-treated group), serum CK elevated slightly but did not exceed 10-fold basal value (except in one rabbit of Group III at the 6th week). Serum levels of ALP, creatinine, BUN, and electrolytes remained normal in all groups, while serum transaminase values paralleled serum CK: values in Group I were higher than those in Groups II and III.

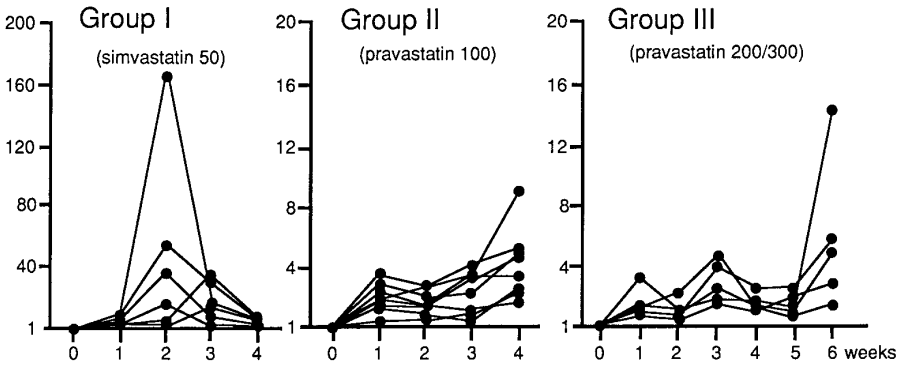

FIG. 1. Changes of serum CK levels in rabbits. The values are expressed as the multiple of pretreatment basal level.

Electrophysiologic Study (Table 2)

Electrical discharges typical of myotonia were observed in some rabbits of Groups I and III. All rabbits in Group I showed myotonic discharges by the 3rd week, while two of five rabbits in Group III showed myotonic discharges by the 6th week. No other indications of myogenic or neurogenic changes were observed in any rabbits.

Morphologic Findings (Table 3)

In Group I, four of six rabbits showed myopathic changes. Four rabbits showed mild myopathic change, including degenerating fibers and uneven fiber size in SOL muscles. One rabbit showed very severe myopathic change, including several necrotic and degenerating fibers, marked alteration of fiber size, and increased central nucleus in EDL muscle (Figs. 2A and 2B). Some fibers with degeneration and necrosis showed derangement of the oxidative enzyme network and increased acid phosphatase activity. Macrophages were found in necrotic fibers. Fibrous connective tissue remained normal in perimysial and endomysial spaces. There were no ragged-red fibers in the modified Gomori-trichrome stained sections. Cytochrome c oxidase, ATPase, oil red O, and PAS stains appeared normal. The rabbits in Groups II and III showed less severe changes. One rabbit in Group II showed few degenerating fibers, and two rabbits in Group III showed mild to moderate myopathic changes with muscle fiber degeneration and necrosis. Neurogenic changes were not observed in any of the groups. Toluidine blue sections of severely degenerated muscle revealed the hypercontraction in some areas of the muscle fiber (Figs. 2C and 2D) and gathering of a few number of small vacuoles (Figs. 2E and 2F).

The muscle fiber ultrastructure was destroyed in severely degenerated fibers. In slightly degenerated fibers, myofibrils either partly disappeared or showed increase of glycogen granules and accumulation of degeneration product in subsarcolemmal spaces (Figs. 3A–3C). In some fibers, swollen mitochondria and autophagic vacuoles were found among the myofibrils and in the subsarcolemmal spaces (Figs. 3A and 3D). No bizarre-shaped mitochondria nor crystalline inclusion bodies in mitochondria were found. These findings were observed in both SOL and EDL muscles. Accumulation of lipid droplets or disruption of basal membrane of muscle fiber were not detected.

Ubiquinone Contents (Table 4)

Ubiquinone content in muscle decreased in all three groups compared to controls. The levels of reduction were 22 to 36% in Group I, 18 to 52% in Group II, and 49 to 72% in Group III.

TABLE 2
Electrical Myotonic Discharges in Rabbits

	Week						
	0	1	2	3	4	5	6
Group I (n = 6)							
(simvastatin 50)	(—)	(—)	4/6	6/6	4/6		
Group II (n = 8)							
(pravastatin 100)	(—)	(—)	(—)	(—)	(—)		
Group III (n = 5)							
(pravastatin 200/300)	(—)	(—)	(—)	(—)	(—)	(—)	2/5

Note. Results are expressed as the number of rabbits that showed myotonic discharges/total number of rabbits.

TABLE 3
Morphologic Findings in Rabbits

		SOL	EDL	Morphologic findings
Group I (simvastatin 50)				
(n = 6)	+	4/6	0/6	Degenerating fibers
	++	0/6	0/6	
	+++	0/6	1/6	Degenerating/necrotic fibers
Group II (pravastatin 100)				
(n = 8)	+	1/8	0/8	Degenerating fibers
	++	0/8	0/8	
	+++	0/8	0/8	
Group III (pravastatin 200/300)				
(n = 5)	+	1/5	0/5	Necrotic fibers
	++	1/5	0/5	Degenerating/necrotic fibers
	+++	0/5	0/5	

Note. Results are expressed as the number of rabbits that showed morphological changes/total number of rabbits. Morphologic changes of muscles were rated as follows: +, less than 10 degenerating/necrotic fibers/1000 fibers studied; ++, 10 to 20 degenerating/necrotic fibers/1000 fibers studied; and +++, more than 20 degenerating/necrotic fibers/1000 fibers studied.

Ubiquinone content in heart, liver, and kidney also decreased in all three groups but were less so compared to skeletal muscle. Conversely, ubiquinone contents in cerebrum and cerebellum increased slightly in all three groups.

Mitochondrial Enzyme Activities (Table 5)

Mitochondrial enzyme activities of NADH–cytochrome c reductase, succinate-cytochrome c reductase, cytochrome c oxidase, and citrate synthase were normal in all three groups.

DISCUSSION

Experimental myopathy induced by HCR inhibitors have been confirmed in rabbits (Nakahara *et al.*, 1992; Fukami *et al.*, 1993) and in rats (Smith *et al.*, 1991; Waclawik *et al.*, 1993). In our earlier study of simvastatin-induced myopathy in rabbits (Nakahara *et al.*, 1992), we found the following: (1) high serum levels of CK; (2) necrotic or degenerating fibers; and (3) myotonic discharges on EMG. Rhabdomyolysis has been reported in people given lovastatin or simvastatin, and myositis was reported in a patient given pravastatin. Electrical or clinical myotonia has not been reported in humans given these drugs (London *et al.*, 1991).

Although simvastatin at 50 mg/kg/day was found to be as effective in reducing serum cholesterol level as pravastatin at 100 mg/kg/day, the potential for producing myopathy was greater for simvastatin than pravastatin. Electrical myotonia was found in all rabbits treated with simvastatin (Group I) and in only two rabbits treated with pravastatin at high dosage (Group III). High serum CK levels (>10-fold above basal pretreatment levels), with or without muscle necrosis, were induced in four of six rabbits treated with simvastatin (Group I) but in only one of five rabbits receiving pravastatin (Group III). At toxic doses, pravastatin and simvastatin seemed to have similar actions in skeletal muscle: pravastatin at high enough dosage eventually induced both electrical myotonia and serum CK elevation. The marked difference of myotoxicity between simvastatin and pravastatin suggested that the myopathy did not result from reduced serum cholesterol levels, but by another mechanism. Electrical myotonia, indicating hyperexcitability of muscle surface membrane, was more frequently induced by lipophilic simvastatin than by hydrophilic pravastatin. The differences in chemical character of the drugs may be responsible for differences in dosage required for myotoxicity in rabbits.

Ubiquinone transfers electron from flavin-linked dehydrogenase of complex I or complex II to cytochrome bc1 complex (complex III). The ubiquinone activity as a mobile carrier of reducing equivalents in mitochondrial respiratory chain is measured by determining the enzyme activities of NADH–cytochrome c reductase and succinate–cytochrome c reductase. Ubiquinone content decreased in skeletal muscle by 22 to 36% in Group I, by 18 to 52% in Group II, and by 49 to 72% in Group III. However, the activities of NADH–cytochrome c reductase and succinate–cytochrome c reductase were normal in all three groups of rabbits. This included several rabbits showing muscle necrosis with elevated serum CK levels and electrical myotonia. We conclude that the function of ubiquinone as an electron transporter in mitochondrial respiration remained normal, in spite of its decreased content. Thus, one infers that the myopathy was not the consequence of a disturbed mitochondrial respiratory function. Moreover, we did not find histochemical ragged-red fibers characteristic of disturbed mitochondrial respiration.

Extreme deficiency of ubiquinone can cause mitochondrial dysfunction. In a patient with mitochondrial encephalomyopathy associated with deficiency of ubiquinone biosynthesis, muscle ubiquinone content was 3.7% of control values, with

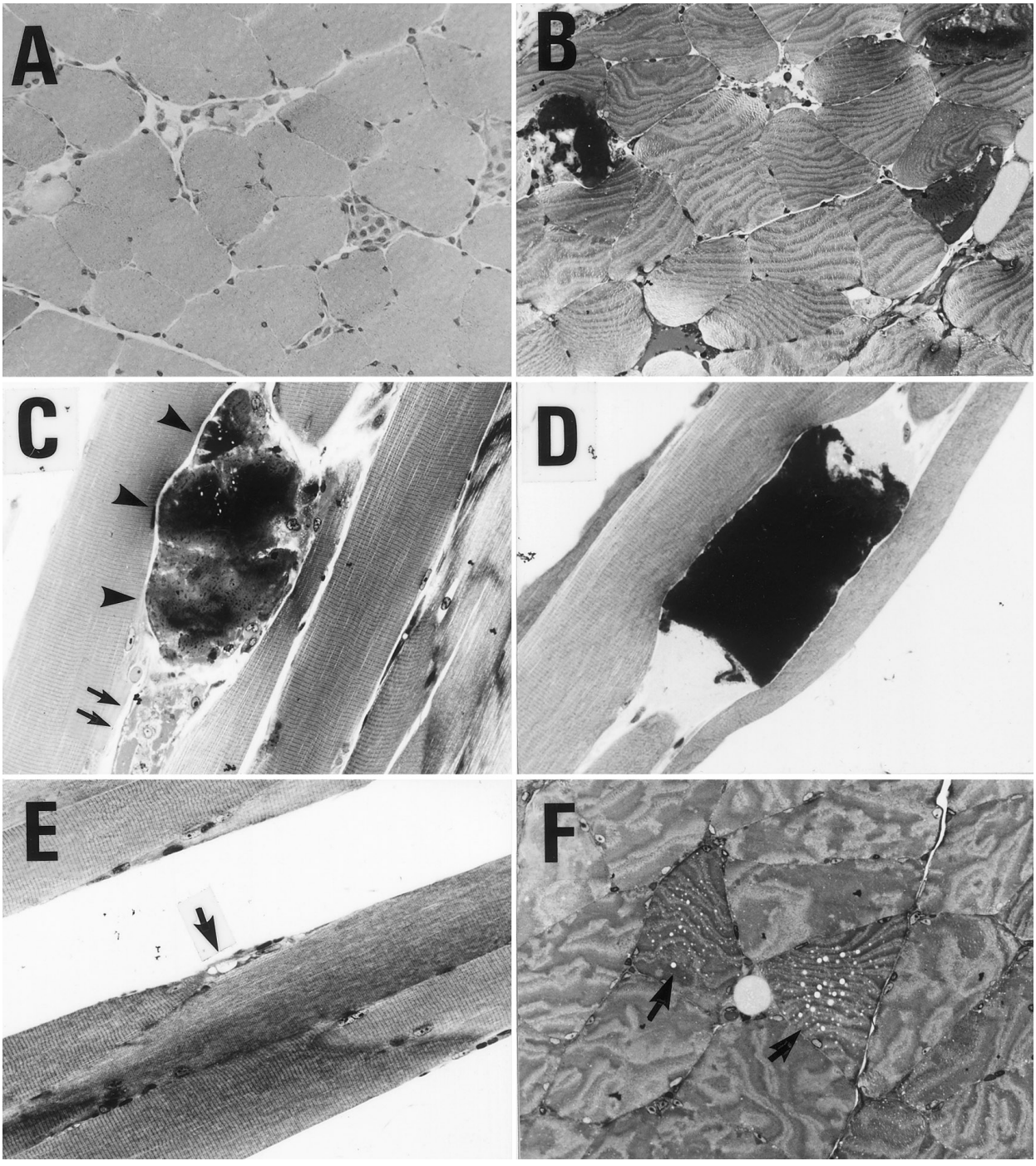

FIG. 2. The histochemical findings. All findings here are from SOL or EDL muscles in the severely affected rabbits of Group I. (A and B) Severe myopathic changes with several degenerating and necrotic fibers are observed. Macrophages invaded some necrotic fibers, and a few small vacuoles are scattered in some degenerating fibers. A; H&E staining, 66×, B; toluidine blue staining, 66×). (C) A part of muscle fiber shows hypercontraction (arrowheads) with the necrotic area invaded by macrophages (arrows) (toluidine blue staining, 66×). (D) Both ends of hypercontracted muscle fiber becomes amorphous (toluidine blue staining, 100×). (E and F) Formation of microvacuoles is observed (arrow) (toluidine blue staining, 100×).

low activities of complex I-III (NADH–cytochrome c reductase) and complex II-III (succinate–cytochrome c reductase) (Ogasawara *et al.*, 1989). However, exposure of cultured neuroblastoma cells to mevinolin (lovastatin) resulted in a 40 to 57% decline of ubiquinone content in mitochondria without affecting respiratory function (Maltese and Aprille, 1985). These findings indicate that mitochondrial respiration could be preserved in states of moderate reduction of ubiquinone con-

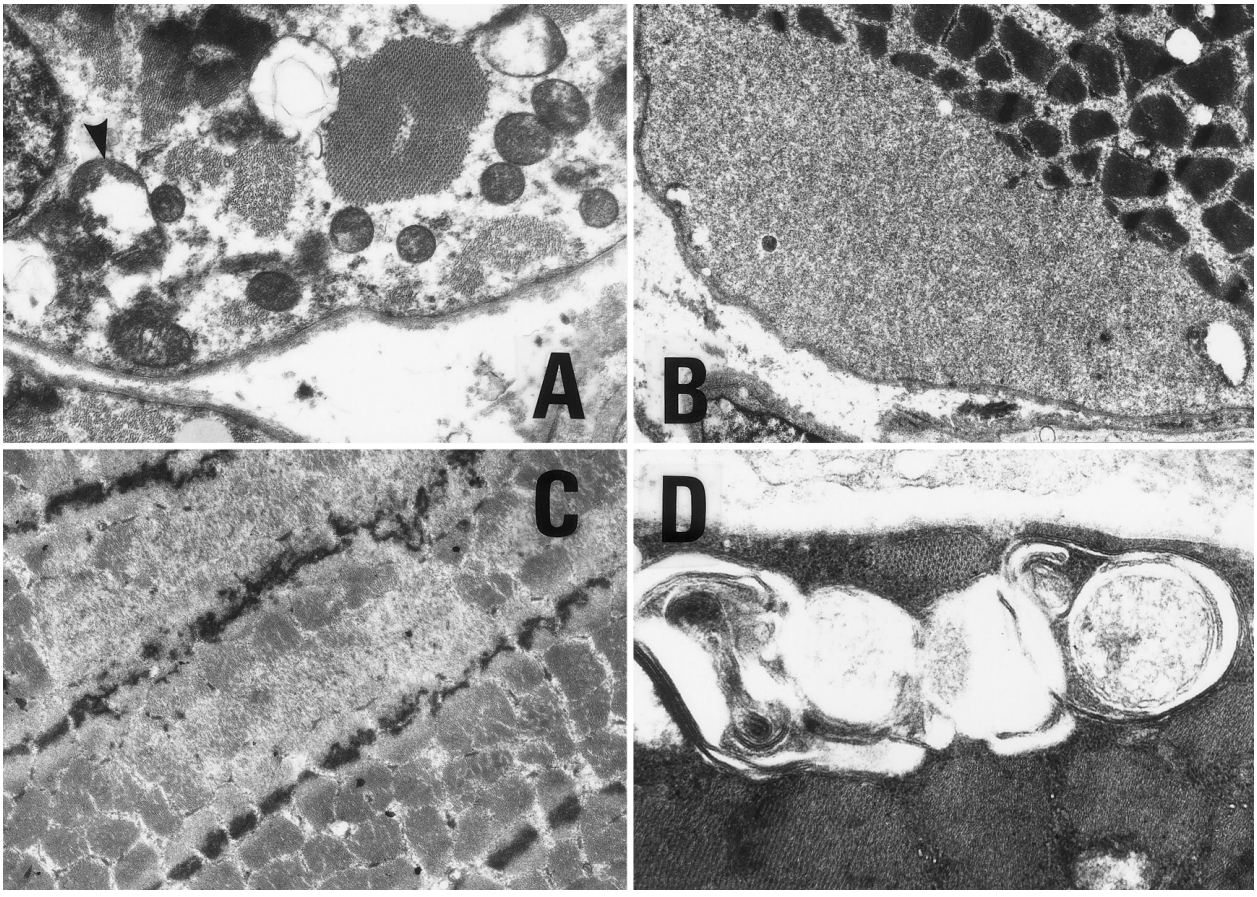

FIG. 3. The electron microscopic findings. (A) Several membranous vacuoles and swollen mitochondria with disrupted cristae (arrowhead) are observed (8300×). (B) The degeneration product are accumulated in subsarcolemmal areas (3300×). (C) The disruption of myofibrils and derangement of Z band are shown (3300×). (D) Several microvacuoles with or without myeloid figures are shown in the muscle fibers (13,000×).

tent. Eukaryotic cells probably have sufficient reserves of ubiquinone to maintain mitochondrial respiratory function in the course of drug treatment.

A possible pathomechanism of the myopathy may result from damaging of the membrane. Waclawik *et al.* (1993) reported an experimental myopathy in rats induced by lova-

TABLE 4
Total Amounts of Ubiquinone in Rabbits

	Group I (simvastatin 50) (n = 6)	Group II (pravastatin 100) (n = 8)	Group III (pravastatin 200/300) (n = 5)	Control (n = 6)
Skeletal muscle				
SOL	25.9 ± 7.8 (−22)	27.2 ± 5.7 (−18)	17.1 ± 4.4 (−49)***	33.2 ± 6.6
EDL	12.2 ± 2.4 (−24)	11.8 ± 2.0 (−27)	4.8 ± 2.7 (−70)*	16.1 ± 9.1
Anterotibialis	21.6 ± 5.1 (−36)***	20.1 ± 6.1 (−40)***	13.3 ± 1.0 (−60)***	33.2 ± 6.4
Gastrocunemius	13.8 ± 4.7 (−36)*	10.2 ± 2.3 (−52)***	5.9 ± 2.5 (−72)***	21.5 ± 6.0
Heart	138.7 ± 12.5 (−23)*	155.4 ± 31.2 (−14)	133.0 ± 12.8 (−27)***	181.0 ± 21.4
Liver	28.4 ± 4.8 (−20)*	30.3 ± 4.3 (−15)	32.4 ± 8.7 (−9)	35.6 ± 5.1
Kidney	68.3 ± 9.2 (−19)**	70.4 ± 4.2 (−17)***	66.5 ± 12.3 (−21)*	84.3 ± 7.5
Cerebrum	19.5 ± 1.9 (+5)	20.5 ± 0.8 (+10)	20.2 ± 1.2 (+8)	18.7 ± 3.0
Cerebellum	18.5 ± 1.5 (0)	19.1 ± 1.7 (+3)	21.1 ± 2.6 (+16)	18.5 ± 3.1

Note. Values are μg/g wet wt tissue. Values in parentheses are percentages. ***$p < 0.005$; **$p < 0.01$; *$p < 0.05$; Student's t-test.

TABLE 5
Mitochondrial Enzyme Activity in Muscles

Mitochondrial enzyme	Group I (simvastatin 50) (n = 6)	Group II (pravastatin 100) (n = 8)	Group III (pravastatin 200/300) (n = 5)	Control (n = 6)
SOL				
NADH-CCR	2.82 ± 1.06	2.28 ± 0.82	2.86 ± 1.06	3.04 ± 1.30
Succinate-CCR	2.84 ± 1.11	1.82 ± 0.98	2.57 ± 1.33	2.46 ± 0.99
CCO	4.61 ± 1.48	3.78 ± 1.92	4.37 ± 2.67	4.54 ± 1.14
Citrate Synthase	22.2 ± 5.80	17.2 ± 5.84	21.7 ± 5.72	20.8 ± 4.19
EDL				
NADH-CCR	0.54 ± 0.28	0.64 ± 0.43	0.65 ± 0.20	0.53 ± 0.21
Succinate-CCR	1.27 ± 0.69	0.93 ± 0.27	1.12 ± 0.33	0.85 ± 0.33
CCO	1.39 ± 0.55	2.75 ± 1.98	1.82 ± 1.26	1.41 ± 0.95
Citrate Synthase	10.6 ± 3.23	9.47 ± 3.17	8.52 ± 0.75	9.06 ± 3.85

Note. Values are expressed as μmol/min/g wet wt tissue.

statin. They found morphologic changes in membranous organelles of mitochondria and sarcoplasmic reticulum, microvacuole formation, and occurrence of several hypercontracted fibers in gastrocnemius muscle but not in SOL muscle. Their speculation was that myopathy was not caused by the mitochondrial dysfunction, but by the involvement of sarcoplasm and organelle membrane. In this present experiment, the morphologic change of membranous organelles and the formation of autophagic vacuoles were observed in both of SOL and EDL muscles. Autophagic vacuoles might be secondarily formed on the process of muscle fiber degeneration. Increased activity of acid phosphatase supported the active degenerative process in lysozyme. In the present study, the hypercontraction of muscle fibers should be emphasized as another prominent and characteristic finding, suggesting the hyperexcitability of muscle membrane or abnormal increase of cytosolic calcium ion.

In our separate works, we reported that HCR inhibitors induced myotonia because of chloride conductance (channel) blockage in the muscle membrane (Sonoda *et al.,* 1994). The muscle membrane excitability on an isolated muscle from normal rabbit was produced by the perfusion of HCR inhibitors for at least 20 min and the effect was reversible and cultured rat myoblast stimulated by simvastatin showed the increased cytosolic calcium ion level and thereafter the rapture of cell membrane (Nakahara *et al.,* 1994). Taken together, the muscular disturbances induced by HCR inhibitors strongly suggested a dysfunction of sarcoplasmic membrane, as well as degeneration of membranous organelles, including sarcoplasmic reticulum and mitochondria.

In conclusion, the myopathy presented in this work was not a consequence of muscle mitochondrial respiratory dysfunction. Simvastatin has a greater potential for producing electrical myotonia and rhabdomyolysis than pravastatin in rabbits. The greater myotoxicity may be due to differences in chemical character of HCR inhibitors, including their lipophilicities.

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