Mevinolin and colestipol stimulate receptor-mediated clearance of low density lipoprotein from plasma in familial hypercholesterolemia heterozygotes

(low density lipoprotein receptors/3-hydroxy-3-methylglutaryl-CoA reductase/compactin/bile acid metabolism)

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ABSTRACT In subjects with heterozygous familial hypercholesterolemia (FH), a 50% deficiency of receptors for plasma low density lipoprotein (LDL) impairs the removal of LDL from plasma and produces hypercholesterolemia. In these patients mevinolin, an inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase, blocks cholesterol synthesis and lowers plasma LDL levels. To determine the mechanism for the LDL-lowering effect, we administered [131I]labeled LDL intravenously to six FH heterozygotes before and during treatment with mevinolin and calculated the apparent fractional catabolic rate (FCR) and synthetic rate for LDL. After mevinolin treatment, the mean plasma LDL-cholesterol level declined from 262 to 191 mg/dl (27% decrease), the mean FCR for [131I]labeled LDL increased from 0.30 to 0.41 pools per day (37% increase), and the mean calculated synthetic rate for LDL-protein did not change significantly. In one FH heterozygote with an ileal bypass and in another who received colestipol, the addition of mevinolin caused, respectively, a 41% and 60% decrease in plasma LDL levels and a 60% and 100% increase in the FCR for plasma LDL. The contribution of receptor-dependent pathways to the FCR for plasma LDL was estimated in three FH heterozygotes by simultaneous measurements of the FCR for native [131I]labeled LDL and [125I]labeled glucosylated LDL, which does not bind to LDL receptors. Whereas the removal rate for native LDL increased after mevinolin treatment, the removal rate for glucosylated LDL did not change. The current data suggest that mevinolin alone or mevinolin plus bile acid depletion (i.e., ileal bypass or colestipol therapy) decreases plasma LDL levels primarily by raising the number of LDL receptors and, thus, enhancing the removal of LDL from plasma.

Patients with heterozygous familial hypercholesterolemia (FH) have one mutant gene and one normal gene specifying the cell surface receptor for plasma low density lipoprotein (LDL) (1). This receptor normally mediates the cellular uptake and degradation of LDL in liver and extrahepatic tissues. FH heterozygotes produce, on average, one-half the normal number of LDL receptors (1) and remove LDL from plasma at about two-thirds the normal rate (1–3). The apparent synthetic rate for LDL-protein also tends to be increased (1, 2, 4).

In cultured human fibroblasts, the synthesis of LDL receptors is under feedback regulation (5). Under normal conditions of growth, cells from normal subjects and from FH heterozygotes express only about 10% of the maximal number of receptors (6). In FH heterozygote cells, as in normal cells, production of receptor is stimulated when the cells are deprived of exogenous cholesterol and the cellular content of cholesterol (Chol) declines (6). A similar feedback regulation of receptor synthesis appears to operate in vivo. Thus, when FH heterozygotes are treated with the bile acid-binding resin cholestyramine, receptor-mediated catabolism of plasma LDL increases and the level of plasma LDL declines (7). This increase in receptor activity is postulated to result from a decrease in the hepatic content of Chol as a result of cholestyramine’s ability to bind bile acids in the intestine and prevent their reabsorption. This depletion of bile acids stimulates the liver to convert more Chol to bile acids, and this in turn causes the liver to produce an enhanced number of LDL receptors (1).

Another approach to depletion of the hepatic content of Chol has become available through the discovery of a class of fungal metabolites that inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), a rate-controlling enzyme in Chol synthesis. The prototype compound, compactin, and its analogue, mevinolin, lower the plasma LDL level in normal animals (8, 9), normal humans (10), and FH heterozygotes (11–13). In dogs this lowering of LDL is due in part to an enhanced degradation of plasma LDL, which results from an increased production of LDL receptors in the liver (9). In dogs (9) and in humans (13), the combination of a bile acid-binding resin (cholestyramine or colestipol) and a HMG-CoA reductase inhibitor (compactin or mevinolin) produces a much greater decrease of LDL levels than can be obtained by either agent alone. In dogs, this potentiation is due to a synergistic effect of the two drugs in stimulating the production of hepatic LDL receptors (9).

In the current studies, we have sought to determine whether mevinolin alone or in combination with bile acid depletion leads to an enhanced receptor-mediated degradation of LDL in FH heterozygotes. To distinguish between receptor-dependent and receptor-independent catabolic pathways, we have compared the simultaneous clearance of native LDL and LDL that has been modified by glucosylation in vitro. As shown by Kesaniemi et al., glucosylated LDL (Glc-LDL) does not bind to LDL receptors in vitro; therefore, its catabolism can be used as an index of receptor-independent catabolic pathways (14). The current results indicate that mevinolin alone, or together with bile acid depletion, decreases plasma LDL levels in FH heterozygotes by stimulating receptor-mediated LDL catabolism.

METHODS

Patients. Six FH heterozygotes were studied in the General Clinical Research Center at Parkland Memorial Hospital or in

Abbreviations: apo, apoprotein; FCR, fractional catabolic rate; FH, familial hypercholesterolemia; HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-CoA reductase; LDL, low density lipoprotein; Glc-LDL, glucosylated LDL; Chol, cholesterol; LDL-Chol and LDL-protein, Chol and protein associated with the LDL fraction, respectively.
the Metabolic Unit at the Veterans Administration Medical Center (Dallas, TX). The subjects were given a partial solid-food diet with a calorie distribution of 40% fat (polyunsaturated-to-saturated ratio of 0.33), 40% carbohydrate, and 20% protein. Chol intake was limited to 250 mg/day.

**Drug Therapy.** Capsules of mevinolin and placebo were supplied by Merck Sharp and Dohme (courtesy of J. Tobert). Mevinolin was given orally (20 mg twice daily). Colestipol (Upjohn) was given orally (10 g twice daily). Two patients (J. P. and M. B.) were first studied during a placebo (control) period, followed by mevinolin treatment. Two patients (J. C. and M. B.) were first studied during mevinolin treatment followed by a placebo period. One patient (T. F.) was studied four times (see Fig. 4). One patient (C. C.) was studied three times (see Fig. 6). Each study lasted 5–6 weeks. The protocol was approved by the U.S. Food and Drug Administration and by the Human Research Review Boards of the University of Texas Science Center and Veterans Administration Medical Center. Informed consent was obtained from each patient.

**Lipoprotein Turnover Studies.** Two to 3 weeks after starting placebo or drug therapy, plasma was obtained from each patient, and LDL (density 1.019–1.063 g/ml) was isolated by ultracentrifugation and sterilized by Millipore filtration (15). One aliquot (14 mg of LDL-protein) was incubated in 1.7 ml of 200 mM D-glucose/30 mM sodium cyanoborohydride/10 mM sodium phosphate, pH 7.4/0.14 M sodium chloride/0.003% EDTA (16). After Millipore filtration, the mixture was incubated at 37°C in a sealed plastic tube for 48 hr and dialyzed at 4°C against 6 liters of 0.15 M NaCl/0.01% EDTA, pH 7.4. After repeat Millipore filtration, 5 mg of Glc-LDL was radiolabeled with 125I (Glc-125I-LDL) (15). A second aliquot of the original LDL (5 mg of LDL-protein) was kept at 4°C for 60–70 hr and then radiolabeled with 131I (131I-LDL) (15). Native 125I-LDL and Glc-125I-LDL were sterilized by Millipore filtration, mixed, and injected into rabbits for pyrogen testing (3, 15) and comparison of turnover rates (17).

Each turnover study was initiated by the intravenous injection of 2 ml of a mixture of native 131I-LDL (50 μCi; 0.3 mg of LDL-protein; 1 Ci = 3.7 × 1010 Bq), Glc-125I-LDL (50 μCi; 0.2 mg of LDL-protein), unlabeled native LDL (3 mg), and human serum albumin (150 mg). Kinetic parameters for disappearance of LDL were calculated by the two-pool model of Matthews (18). The apoprotein concentration of LDL (apo-LDL) was calculated from the measured value for Chol associated with the LDL fraction (LDL-Chol) and the measured ratio of protein to Chol in each subject’s LDL (2, 15).

**RESULTS**

All of the patients had family histories consistent with FH and plasma levels of LDL-Chol in the heterozygote range (Table 1).

Five of the six subjects had tendon xanthomata and two had clinical signs of coronary heart disease. One patient (C. C.) had undergone an ileal bypass 4 years prior to the current study. The subjects were fed a low Chol diet (250 mg/day) and treated with placebo or drugs for 2–3 weeks on a metabolic ward prior to the turnover study. Diet and drug therapy were continued throughout the turnover study, which lasted 3 weeks.

Table 2 and Fig. 1 summarize the findings with regard to the kinetic parameters of 131I-LDL metabolism. For comparative purposes, we have included results obtained previously in 16 normal healthy subjects studied by us with a similar LDL turnover technique while they were consuming the same low Chol diet under the same metabolic ward conditions (2, 15). The 16 normal subjects are not strictly comparable to the FH heterozygotes in that the normal subjects were younger (mean age = 23 years).

During the placebo period, mean plasma LDL-Chol level for the six FH heterozygotes was 262 mg/dl, which is 3-fold higher than the level in the normal young subjects. After treatment for 3–6 weeks with mevinolin, mean plasma LDL-Chol declined by 27% to 191 mg/dl (P < 0.01). During the placebo period, mean fractional catabolic rate (FCR) for 131I-LDL was 0.30 pools per day in the six FH heterozygotes. After mevinolin treatment, the FCR increased in all subjects. The mean FCR increased by 37% to 0.41 pools per day (P < 0.01). The calculated synthetic rate for apo-LDL during the control period was above normal in five of the six subjects and did not change significantly after mevinolin treatment (Table 2 and Fig. 1).

Fig. 2 shows the results of simultaneous studies of the carboxylation of 131I-LDL and Glc-125I-LDL in one FH heterozygote during the placebo and mevinolin treatment periods. During the placebo period, the FCR for native LDL was 0.29 pools per day. Glc-LDL disappeared from plasma more slowly (0.16 pools per day). The difference between these two clearance rates (0.13 pools per day) presumably represents the receptor-mediated component (14, 17, 19, 20). After treatment with mevinolin, the disappearance of native LDL from plasma was accelerated (FCR = 0.48 pools per day). On the other hand, there was no increase in the rate of removal of Glc-LDL (FCR = 0.18 pools per day). Thus, the increase in clearance of native LDL could be attributed to an increase in receptor-mediated clearance. By these criteria, receptor-mediated FCR increased from 0.13 to 0.30 pools per day on mevinolin.

All six FH heterozygotes received both native 131I-LDL and Glc-125I-LDL, as did the subject in Fig. 2. However, in three of the patients, the Glc-LDL disappeared more rapidly from plasma than did native LDL. Rapid clearance of Glc-LDL in some patients was also observed by Kesaniemi et al. (14). It presumably results from the existence in some human subjects of a clearance mechanism that recognizes Glc-LDL as an abnor-

Table 1. Clinical data on FH heterozygotes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>Plasma Chol, mg/dl</th>
<th>Plasma triglyceride, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>LDL</td>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J.C.‡</td>
<td>32</td>
<td>M</td>
<td>70</td>
<td>164</td>
<td>320 ± 6</td>
<td>281 ± 9</td>
</tr>
<tr>
<td>M.B.‡</td>
<td>36</td>
<td>M</td>
<td>70</td>
<td>169</td>
<td>340 ± 32</td>
<td>272 ± 24</td>
</tr>
<tr>
<td>J.P.‡</td>
<td>37</td>
<td>M</td>
<td>106</td>
<td>182</td>
<td>267 ± 17</td>
<td>207 ± 18</td>
</tr>
<tr>
<td>T.P.‡</td>
<td>45</td>
<td>M</td>
<td>52</td>
<td>186</td>
<td>378 ± 19</td>
<td>340 ± 18</td>
</tr>
<tr>
<td>C.C.‡</td>
<td>52</td>
<td>F</td>
<td>63</td>
<td>162</td>
<td>319 ± 21</td>
<td>228 ± 18</td>
</tr>
<tr>
<td>M.B.a</td>
<td>55</td>
<td>F</td>
<td>131</td>
<td>167</td>
<td>306 ± 11</td>
<td>254 ± 6</td>
</tr>
</tbody>
</table>

M, male; F, female.

*Mean ± 1 SD of six or seven observations made during the course of each turnover study prior to drug treatment.

†J.C. is the daughter of M.B.

‡M.B. and C.C. are first cousins.
Table 2. Kinetic parameters for LDL turnover studies in FH heterozygotes before and during treatment with mevinolin

<table>
<thead>
<tr>
<th>Subject</th>
<th>Treatment</th>
<th>Plasma volume, ml</th>
<th>LDL-Chol, mg/dl</th>
<th>LDL-protein, mg/dl</th>
<th>t1/2 for exponential decay, days</th>
<th>FCR, pools per day</th>
<th>apo-LDL synthesis and catabolism mg/day</th>
<th>apo-LDL distribution, % TVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.C.</td>
<td>Control</td>
<td>2,168</td>
<td>281</td>
<td>188</td>
<td>1.21 ± 0.25</td>
<td>4.28</td>
<td>0.33</td>
<td>1,345 ± 19.0</td>
</tr>
<tr>
<td></td>
<td>Mevinolin</td>
<td>2,126</td>
<td>201</td>
<td>142</td>
<td>1.32 ± 0.28</td>
<td>4.78</td>
<td>0.37</td>
<td>1,117 ± 16.1</td>
</tr>
<tr>
<td>M.B.</td>
<td>Control</td>
<td>2,524</td>
<td>272</td>
<td>158</td>
<td>1.65 ± 0.23</td>
<td>4.23</td>
<td>0.29</td>
<td>1,156 ± 16.3</td>
</tr>
<tr>
<td></td>
<td>Mevinolin</td>
<td>2,490</td>
<td>238</td>
<td>138</td>
<td>0.65 ± 0.01</td>
<td>4.01</td>
<td>0.48</td>
<td>1,649 ± 24.2</td>
</tr>
<tr>
<td>J.P.</td>
<td>Control</td>
<td>3,417</td>
<td>207</td>
<td>132</td>
<td>1.83 ± 0.27</td>
<td>4.99</td>
<td>0.27</td>
<td>1,217 ± 11.4</td>
</tr>
<tr>
<td></td>
<td>Mevinolin</td>
<td>3,002</td>
<td>156</td>
<td>106</td>
<td>1.41 ± 0.34</td>
<td>3.94</td>
<td>0.36</td>
<td>1,145 ± 10.8</td>
</tr>
<tr>
<td>T.P.</td>
<td>Control 1</td>
<td>2,397</td>
<td>340</td>
<td>264</td>
<td>1.54 ± 0.28</td>
<td>5.29</td>
<td>0.25</td>
<td>1,402 ± 27.3</td>
</tr>
<tr>
<td></td>
<td>Control 2</td>
<td>2,139</td>
<td>318</td>
<td>242</td>
<td>1.14 ± 0.33</td>
<td>4.33</td>
<td>0.33</td>
<td>1,708 ± 31.9</td>
</tr>
<tr>
<td></td>
<td>Control avg</td>
<td>2,268</td>
<td>329</td>
<td>238</td>
<td>1.34 ± 0.61</td>
<td>4.81</td>
<td>0.29</td>
<td>1,555 ± 29.6</td>
</tr>
<tr>
<td></td>
<td>Mevinolin</td>
<td>2,424</td>
<td>208</td>
<td>158</td>
<td>1.15 ± 0.21</td>
<td>4.17</td>
<td>0.36</td>
<td>1,420 ± 26.7</td>
</tr>
<tr>
<td>C.C.</td>
<td>Control</td>
<td>2,123</td>
<td>228</td>
<td>205</td>
<td>1.62 ± 0.26</td>
<td>5.54</td>
<td>0.33</td>
<td>1,436 ± 23.2</td>
</tr>
<tr>
<td></td>
<td>Mevinolin</td>
<td>1,939</td>
<td>152</td>
<td>125</td>
<td>1.12 ± 0.27</td>
<td>3.67</td>
<td>0.46</td>
<td>1,114 ± 18.0</td>
</tr>
<tr>
<td>M.Ba.</td>
<td>Control</td>
<td>3,813</td>
<td>254</td>
<td>193</td>
<td>1.26 ± 0.38</td>
<td>4.13</td>
<td>0.28</td>
<td>2,061 ± 15.8</td>
</tr>
<tr>
<td></td>
<td>Mevinolin</td>
<td>3,262</td>
<td>190</td>
<td>121</td>
<td>1.08 ± 0.03</td>
<td>4.03</td>
<td>0.46</td>
<td>1,657 ± 14.4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Control</td>
<td>2,719 ± 719</td>
<td>262 ± 43</td>
<td>186 ± 37</td>
<td>1.49 ± 0.25</td>
<td>4.66 ± 0.55</td>
<td>0.55 ± 0.03</td>
<td>1,462 ± 327 ± 9.2 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>Mevinolin</td>
<td>2,533 ± 504</td>
<td>191 ± 33</td>
<td>132 ± 18</td>
<td>1.12 ± 0.28</td>
<td>4.10 ± 0.37</td>
<td>0.41 ± 0.05</td>
<td>1,350 ± 261 ± 8.4 ± 6.0</td>
</tr>
<tr>
<td>P values</td>
<td></td>
<td>0.16</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.065</td>
<td>0.16</td>
<td>&lt;0.01</td>
<td>0.43 ± 0.06</td>
</tr>
<tr>
<td>Normals**</td>
<td>Control</td>
<td>2,768 ± 680</td>
<td>84 ± 15</td>
<td>45 ± 9</td>
<td>1.08 ± 0.19</td>
<td>4.14 ± 0.47</td>
<td>0.43 ± 0.06</td>
<td>551 ± 120 ± 8.5 ± 1.4</td>
</tr>
</tbody>
</table>

*Mean of six or seven separate measurements made during the course of each turnover study.

†These data represent the t1/2 of the first (1) and second (2) exponentials of the plasma decay curve.

‡Fraction of the intravascular apo-LDL pool catabolized each day, calculated from the two exponentials of the plasma decay curve.

§Average (avg) of values for control 1 and control 2. The control 1 and control 2 studies were carried out before and after the mevinolin study, respectively.

¶Average (avg) of values for control 1 and control 2. The control 1 and control 2 studies were carried out before and after the mevinolin study, respectively.

**Statistical analyses were performed by paired t analysis using the Interactive Statistical Program developed at the University of Texas Health Science Center at Dallas.

††From references 2 and 15; n = 16.

Fig. 1. LDL-Chol level (A), FCR for plasma LDL (B), and synthetic rate for apo-LDL (C) in six FH heterozygotes before (—) and during (+) treatment with mevinolin. Mean values are summarized in Table 2. The shaded area shows the mean and range for values on 16 normal subjects. *, One FH heterozygote (C.C.) who had an ideal bypass at the time of the study.

Fig. 2. Plasma decay curves after the intravenous injection of native 125I-LDL and Glc-131I-LDL in an FH heterozygote before and during treatment with mevinolin. Two studies of the simultaneous turnover of native 125I-LDL (A, •) and Glc-131I-LDL (C, ○) were performed in patient M.B. The first study was done during mevinolin treatment (A, •), followed by a second study during the placebo period (C, ○).
was added. The calculated synthetic rate for apo-LDL did not change significantly throughout the study. Fig. 5 shows the decay curves for the four sequential LDL turnover studies.

A similar potentiation of mevinolin's action was seen when the drug was administered to a 52-year-old FH heterozygote (C.C.), who had undergone an ileal bypass (Fig. 6). This procedure, like colestipol, blocks bile acid reabsorption. The ileal bypass lowered plasma LDL-Chol from 266 to 228 mg/dl. Addition of mevinolin lowered LDL further to 153 mg/dl and raised the FCR for plasma $^{131}$I-LDL into the normal range (0.46 pools per day). The calculated synthetic rate for apo-LDL increased after ileal bypass and declined after mevinolin was added.

Mevinolin was tolerated well by all of the patients, and no abnormalities were noted in the hemogram, liver function tests, electrolytes, blood urea nitrogen, or serum creatinine.

**DISCUSSION**

In the current studies, we have used the plasma $^{131}$I-LDL turnover technique to determine whether mevinolin alone or mevinolin with bile acid depletion enhances production of LDL receptors in subjects with heterozygous FH. Although the LDL turnover technique is the only method available for use in humans, it is an indirect method that has certain theoretical limitations, as discussed below. Nevertheless, earlier studies in dogs by Kovanen et al. validated this procedure for estimation of LDL receptors through the demonstration that an increase in calculated FCR for intravenously administered $^{131}$I-LDL was correlated with a parallel increase in LDL receptor activity in the liver, as determined by direct binding assays with isolated hepatic membranes (9).

In the current studies, mevinolin caused an increase in the FCR for intravenously administered $^{131}$I-LDL in six FH heterozygotes, and this effect was enhanced when mevinolin was administered together with a bile acid depletion regimen. In the light of the previous data in dogs, the current findings are consistent with the hypothesis that an increase in LDL receptors is a major mechanism for mevinolin's effect in diminishing plasma LDL levels in FH heterozygotes. To test this hypothesis further, we performed double-label studies in which native $^{131}$I-LDL and Glc-$^{131}$I-LDL were administered simultaneously.

**FIG. 3.** Total FCR (A), nonreceptor component of the FCR (B), and receptor component of the FCR (C) in three FH heterozygotes before (-) and during (+) mevinolin treatment. Simultaneous turnover studies of native $^{131}$I-LDL and Glc-$^{131}$I-LDL were performed as described in Fig. 2. Each symbol represents a separate FH heterozygote (\(\square\), C.C.; \(\triangle\), M.B.; \(\odot\), T.P.). Total FCR was derived from turnover of native $^{131}$I-LDL. Nonreceptor component of the FCR was derived from turnover of Glc-$^{131}$I-LDL. The receptor component of FCR was calculated by subtracting nonreceptor FCR from total FCR. * One FH heterozygote (C.C.) who had an ileal bypass at the time of the study.

**FIG. 4.** Effect of combined treatment with mevinolin and colestipol on the plasma LDL-Chol level (A), FCR for plasma LDL (B), and synthetic rate for apo-LDL (C) in an FH heterozygote. The subject (T.P.) was studied in the following sequence: placebo (\(\square\)), mevinolin (\(\Box\)), mevinolin plus colestipol (\(\mathbf{\Box}\)), and placebo (\(\mathbf{\square}\)). The horizontal lines denote the range of values for 16 normal subjects. The decay curves for the turnover of $^{131}$I-LDL are shown in Fig. 5.

**FIG. 5.** Plasma decay curves after the intravenous injection of native $^{131}$I-LDL in an FH heterozygote after various treatments. The subject (T.P.) was studied on four sequential occasions as described in Fig. 4.

**FIG. 6.** Effect of combined treatment with mevinolin and ileal bypass on the plasma LDL-Chol (A), FCR for plasma LDL (B), and synthetic rate for apo-LDL (C) in an FH heterozygote. The subject (C.C.) was studied in the following sequence: no treatment (\(\square\)), surgical creation of an ileal bypass (\(\mathbf{\square}\)), and mevinolin after surgical creation of an ileal bypass (\(\mathbf{\mathbf{\Box}}\)). The horizontal lines denote the range of values for 16 normal subjects.
In the three FH heterozygotes in whom the data could be analyzed, the results indicated that mevinolin selectively increased the receptor-mediated clearance of native LDL without affecting receptor-independent clearance.

The current data support the previous suggestion that the plasma level of LDL can be decreased in FH heterozygotes by agents that deplete the liver of Chol and thereby stimulate the single normal gene to produce an increased number of LDL receptors (21). Moreover, the data suggest that the combination of bile acid depletion (produced by bile acid-binding resins or ileal bypass) and inhibition of HMG-CoA reductase (mevinolin or compactin) has a potentiating effect in increasing LDL receptors and in decreasing plasma LDL levels. Consistent with this formulation is the recent report of Mabuchi et al., who observed a 53% decrease in plasma LDL levels after administration of compactin and cholestyramine (a bile acid-binding resin) to 10 FH heterozygotes, which was much greater than observed with either agent alone (13). A similar 60% decrease in plasma LDL was observed in the FH heterozygote in the current study who received combined mevinolin/cholesteryl therapy (Fig. 4).

As discussed above, the empirical correlation between the FCR [as calculated from the two-pool model of Matthews (18)] and hepatic LDL receptor activity [as measured directly in dogs (9)] allows one to conclude indirectly that mevinolin and cholesteryl increase LDL receptor activity. However, the physiological significance of the two components of the decay curve for plasma LDL is not understood (Table 2 and Fig. 2), and this uncertainty limits further analysis of the data. Some of the heterogeneity in the decay curve may be related to the presence of at least two types of functionally distinct particles within the LDL fraction, one of which is cleared more rapidly than the other (22). Because the pool size for each of these component particles is not known, calculation of an absolute value for the synthetic rate for apo-LDL is subject to error. The synthetic rates presented in this paper and in other literature on this subject represent apparent synthetic rates calculated on the assumption that LDL is a homogenous particle that is distributed in two metabolic pools. Because this assumption may not be valid (22), the calculated synthetic rates should be interpreted with caution. From the current data, we cannot be certain that mevinolin did not change the absolute synthetic rates for the different types of particles contained within the LDL fraction. Indeed, in dogs mevinolin did appear to decrease the synthetic rate for apo-LDL (9).

The reason why some FH heterozygotes clear Glc-LDL from plasma more rapidly than native LDL remains to be explored. Rapid clearance of Glc-LDL is not restricted to FH heterozygotes because some subjects without FH show rapid clearance (14). In the current studies, each patient received Glc-LDL on at least two occasions. All three subjects who cleared Glc-LDL rapidly on the first occasion also cleared it rapidly on the second occasion. On the other hand, the three subjects who cleared Glc-LDL slowly the first time also cleared it slowly on the second occasion. Thus, the factor that determines whether a given individual clears Glc-LDL rapidly or slowly from the circulation may be a genetic polymorphism rather than an environmental variable.

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