Brain Cholesterol Synthesis in Mice Is Affected by High Dose of Simvastatin but Not of Pravastatin

Karin M. Thelen, Katharina M. Rentsch, Ursula Gutteck, Maura Heverin, Maria Olin, Ulla Andersson, Arnold von Eckardstein, Ingemar Björkhem, and Dieter Lütjohann

ABSTRACT

On a global scale, there is an increasing tendency for a more aggressive treatment of hypercholesterolemia. Minor effects of statins on brain cholesterol metabolism have been reported in some in vivo animal studies, and it seems that this is due to a local effect of the drug. We treated male mice of the inbred strain C57/BL6 with a high daily dose of lipophilic simvastatin (100 mg/kg b.wt.) or hydrophilic pravastatin (200 mg/kg b.wt.) or vehicle (controls) by oral gavage for 3 days. To compare the impact of both statins on brain cholesterol synthesis and degradation, levels of cholesterol, its precursor lathosterol, and its brain metabolite 24(S)-hydroxycholesterol as well as statin concentrations were determined in whole-brain lipid extracts using mass spectrometry. The expression of 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase mRNA and of other target genes were evaluated using real-time reverse transcription-polymerase chain reaction. In addition, analysis of liver and serum samples was performed. Similar levels of simvastatin and pravastatin were detected in whole-brain homogenates. Cholesterol contents in the brain, liver, and serum were not affected by high-dose statin treatment. Whereas brain cholesterol precursor levels were reduced in simvastatin-treated animals only, no effect was observed on the formation of the brain cholesterol metabolite, 24(S)-hydroxycholesterol. Polymerase chain reaction analysis revealed that mRNA expression of HMG-CoA reductase and ATP-binding cassette transporter A1 (ABCA1) was significantly up-regulated in simvastatin-treated animals compared with pravastatin-treated or control animals. We conclude that, under the present experimental conditions, brain cholesterol synthesis is significantly affected by short-term treatment with high doses of lipophilic simvastatin, whereas whole-brain cholesterol turnover is not disturbed.

Statins are first-line therapy in the treatment of cholesterol-induced atherosclerotic cardiovascular diseases (Grundy et al., 2004). They are structural analogs of mevalonate and affect, as 3-hydroxymethyl-3-glutaryl (HMG)-coenzyme A (CoA) reductase (CoAR) inhibitors, the rate-limiting step in the cholesterol biosynthesis cascade. They inhibit conversion of HMG-CoA to mevalonate by competitive blocking of the responsible enzyme, HMG-CoAR. The endogenous cholesterol synthesis in the liver is remarkably reduced and, consequently, levels of circulating LDL cholesterol are decreased due to the increasing number of LDL receptors on cell surfaces (Brown and Goldstein, 1981).

Within the past few years plasma cholesterol has been linked to Alzheimer disease pathology, and epidemiological data suggest that statin administration could be of benefit in decelerating the incidence of Alzheimer disease (Jick et al., 2000; Wolozin et al., 2000; Rockwood et al.; 2002). Thus, it is of interest whether statins are able to affect cholesterol metabolism in the brain.

Apparently, the ability of simvastatin to permeate through the blood-brain barrier (BBB) seems to be related to its higher lipophilicity (Tsuiji et al., 1993) despite the fact that the active forms of simvastatin and pravastatin have similar chemical structures (Serajuddin et al., 1991). In contrast to pravastatin, applied in its active acid form (sodium salt), simvastatin is an inactive lactone prodrug that is converted in vivo to the active open-ring acid form.

ABBREVIATIONS: HMG, 3-hydroxy-3-methylglutaryl; CoA, coenzyme A; CoAR, coenzyme A reductase; LDL, low-density lipoprotein; BBB, blood-brain barrier; 24(S)-OH-Chol, 24(S)-hydroxycholesterol; CYP46A1, cholesterol 24(S)-hydroxylase; MS, mass spectrometry; GC, gas chromatography; HPRT, hypoxanthine guanine phosphoribosyl transferase; ABCA1, ATP-binding cassette transporter A1; ApoE, apolipoprotein E; CNS, central nervous system.
According to a recent publication both simvastatin and pravastatin were found in cerebral cortex after administration of high dosages. Within 3 weeks, the levels of cholesterol were significantly reduced (Johnson-Anuna et al., 2005).

Cholesterol synthesis can be evaluated by measurement of mRNA expression levels of HMG-CoA reductase or changes in cholesterol precursors such as lathosterol or its ratio to cholesterol (Björkhem et al., 1987). Cholesterol elimination from the brain can be evaluated by measurement of 24(S)-hydroxycholesterol (24S-OH-Chol) (Björkhem et al., 1999). In contrast to cholesterol, 24S-OH-Chol is able to cross the BBB. The gene responsible for its formation, cholesterol 24(S)-hydroxylase (CYP46A1), may be of key importance for maintenance of cholesterol homeostasis in the brain (Lund et al., 1999).

This study was performed to compare 1) the distribution of simvastatin and pravastatin within the different compartments (brain, liver, and serum) and 2) the effects on cerebral as well as peripheral cholesterol metabolism after short-term, high-dose treatment. The expression of additional target genes in brain and liver samples involved in cholesterol transport and elimination was determined as well.

**Materials and Methods**

**Animals.** The animal experiments were approved by the local animal ethics committee (Karolinska University Hospital, Huddinge, Sweden) in accordance with recommendations of the Federation of European Animal Science Association and European legislation. Male mice of the inbred strain C57BL/6 were given free access to standard rodent diet and water. The animals were alternately maintained in darkness from 6.00 PM to 6.00 AM. Twenty-four mice (3 months of age) were randomized into four groups of six animals each. Each mouse received 250 μl of aqueous pravastatin sodium solution (200 mg/kg b.wt.), simvastatin (100 mg/kg b.wt.), water, or polysorbate 80 (10% g/g in water) by oral gavage twice a day. Simvastatin was purchased from Merck KG (Darmstadt, Germany). Pravastatin was generously donated by Sankyo Co., Ltd., (Tokyo, Japan). Simvastatin was dissolved in polysorbate 80 (10% g/g in water). The dosages of statins used in the present investigation were chosen according to performance in a set of preliminary experiments with three different dosages of pravastatin sodium and simvastatin applied to mice of the same strain, sex, and age. Lower doses of simvastatin or pravastatin had no effect on the levels of lathosterol or expression levels of HMG-CoAR in the brains of those animals (data not shown). The treatment period lasted 3 days. The weight of the animals remained constant within this time. Approximately 6 h after the last administration of the drug or the vehicle, the animals were sacrificed via neck break after anesthesia with carbon dioxide. The animals remained constant within this time. Approximately 6 h after the last administration of the drug or the vehicle, the animals were sacrificed with the use of a quick method described previously (Lütjohann et al., 2004). Dry weight of brain and liver specimens was determined after they were dried to constant weight overnight in a Speedvac (Servant Instruments, Inc., Farmingdale, NY) ultracentrifuge dryer.

**Analysis of Pravastatin and Simvastatin in Brain, Liver, and Serum by GC-MS.** Cholesterol, its precursor lathosterol, its metabolite 24S-OH-Chol, and the plant sterols campesterol and sitosterol were extracted from brain, liver, and serum by chloroform-methanol and determined after derivatization to the corresponding trimethylsilyl ethers by GC-flame ionization detection and GC-MS as reported previously (Lütjohann et al., 2004). Dry weight of brain and liver specimens was determined after they were dried to constant weight overnight in a Speedvac (Servant Instruments, Inc., Farmingdale, NY) ultracentrifuge dryer.

**Lipoprotein and Liver Enzyme Analysis in Serum Samples.** Serum from each animal was assayed for triglycerides, creatinine kinase, alanine aminotransferase, bilirubin, and alkaline phosphatase by routine assays in clinical chemistry.

**Total RNA Preparation and Real-Time Reverse Transcriptase-PCR Analysis.** Total RNA was extracted from frozen liver and brain samples using the Quick Prep Total RNA Extraction Kit (Amersham Biosciences, Buckinghamshire, UK). RNA quality was verified by electrophoresis in a 2.2 M formaldehyde-4-morpholinepro-
Results

The data from both control groups (water and polysorbate) were combined, as no significant differences between the two control groups in the parameters determined (sterols and mRNAs) could be found. However, one simvastatin-treated animal had to be excluded from the statistical evaluations because of extremely high simvastatin concentrations in brain, liver, and serum and increased serum alanine transaminase and bilirubin levels (data not shown). One animal from the pravastatin group and one animal from the simvastatin group had to be excluded from the mRNA expression analyses because of RNA quality impairment.

Concentration and Distribution of Statins and Metabolites in Brain, Liver, and Serum. The efficacy of treatment with statins is commonly proven by monitoring of lipid parameters such as total or LDL cholesterol. Here, we measured concentrations of statins and their metabolites in brain, liver, and serum to examine the amounts and distributions of these compounds within the different compartments and to correlate these data with effects on other markers of cholesterol metabolism.

The concentrations of statins (acids and lactones) showed a broad interindividual range within the different tissues and
serum (Table 1). Although the statins in serum were exclusively present in their active acid forms, simvastatin and pravastatin appeared in brain and liver as lactones and acids. Serum concentrations of the acid and isoacid forms of simvastatin and pravastatin did not differ, despite the fact that 1) the orally applied amount of pravastatin was twice as high as that of simvastatin and 2) the concentrations of total pravastatin (lactone + acid + isoacid) in the liver were on average 3.5-fold higher than those of simvastatin. Assuming that these drugs reach the brain exclusively from the periphery via the serum, we conclude that simvastatin and pravastatin penetrate the BBB to a similar degree in these mice under the conditions presented here.

A high correlation of body weight-corrected simvastatin concentrations was found between brain and liver ($r = 0.967; p = 0.007$), serum and brain ($r = 0.961; p = 0.009$), and serum and liver ($r = 0.937; p = 0.019$). In contrast, no such correlations were found for pravastatin. This finding is consistent with the different distributions of simvastatin and pravastatin in the various compartments.

**Simvastatin Affects Brain Cholesterol Synthesis.** Short-term treatment with high-dose simvastatin as well as pravastatin did not change the levels of cholesterol in whole-brain homogenates (Table 1). Compared with the control group, simvastatin significantly decreased the levels of the cholesterol precursor lathosterol ($-28%; p = 0.002$) as well as its ratio to cholesterol ($-29%; p = 0.002$), indicating a reduction of cholesterol synthesis in the brain. Compared with controls, inhibition of HMG-CoAR was followed by increased mRNA expression levels of HMG-CoAR ($+59%; p < 0.001$) (Table 2). In addition, mRNA expression of the ABCA1 in brains of simvastatin-treated mice was higher than in that in controls ($+48%; p < 0.001$).

Although local concentrations of pravastatin were on average 1.3-fold higher than those found in the brains of simvastatin-treated animals, pravastatin treatment did not decrease the levels of the cholesterol precursor lathosterol or its ratio to cholesterol, nor did it up-regulate levels of HMG-CoAR mRNA expression. Surprisingly, HMG-CoAR mRNA expression levels were even down-regulated ($-29%; p < 0.001$ versus controls). The levels of lathosterol in the brains of simvastatin-treated mice were slightly but significantly lower than those of pravastatin-treated animals ($-20%; p = 0.045$). The mRNA expression levels of HMG-CoA synthase, CYP46A1, and ApoE in the brain were not affected by simvastatin or pravastatin treatment. We can conclude that whole-brain cholesterol turnover does not seem to be affected by short-term, high-dose statin treatment, as levels of cholesterol and its metabolite, 24S-OH-Chol, remained unchanged (Table 1).

**Determination of Plant Sterols in the Different Compartments.** Differences in peripheral plant sterol concentrations after short-term statin treatment were not reflected in the brain. Hence, high-dose statin treatment does not seem to influence the passage of plant sterols across the BBB or their accumulation within this short time interval. The ratios of campesterol to sitosterol in liver and serum did not differ despite the fact that their absolute concentrations are lower in statin-treated animals (Table 1). However, the ratio of campesterol to sitosterol in the brain was significantly higher than the corresponding serum ratios ($6.10 ± 1.65$ versus $3.49 ± 0.26; p < 0.001$). From the latter, we conclude that either 1) the passage of campesterol across the BBB is more favored than it is for sitosterol or 2) the release of sitosterol from the brain is higher than that for campesterol. In any case, the comparison of campesterol and sitosterol concentrations in brain and serum indicates that possible contamination (artifacts) with blood from measurement of whole-brain sterol content is of minor importance.

**Effects of Simvastatin and Pravastatin on Peripheral Cholesterol Metabolism.** High-dose statin treatment did not cause a reduction of cholesterol levels in the liver or in serum (Table 1). Levels of triglycerides in serum were also not affected (data not shown). However, in contrast to the brain, simvastatin treatment did not result in any significant changes in lathosterol levels in the liver, whereas in the serum, the levels of lathosterol were significantly decreased by $33%$ ($p = 0.002$). Nevertheless, there was a significant up-regulation of HMG-CoA reductase mRNA expression in the liver ($+131%; p = 0.019$). Apart from this up-regulation, HMG-CoA synthase mRNA expression ratios were also increased ($+54%; p = 0.019$). The mRNA expression levels of ApoE ($-21%; p < 0.001$), ABCA1 ($-16%; p = 0.019$), and LDL receptor ($-39%; p = 0.019$) were significantly decreased compared with controls after high-dose, short-term treatment with simvastatin. The concentrations of 24S-OH-Chol and the 24S-OH-Chol/cholesterol ratio in the liver were significantly decreased by $24%$ ($p = 0.045$ and $p = 0.035$, respectively) compared with controls.

Mice fed with pravastatin displayed more profound effects on cholesterol synthesis in the liver compared with the effect observed in mice fed with simvastatin. The absolute levels of

**TABLE 2**

Relative expression ratios of mRNAs in the brain and liver after treatment with simvastatin and pravastatin compared with controls ($n = 12$)

<table>
<thead>
<tr>
<th>mRNA Expression Ratios</th>
<th>Brain</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control ($n = 12$)</td>
<td>Simvastatin ($n = 5$)</td>
</tr>
<tr>
<td>HMG-CoA reductase</td>
<td>1.0</td>
<td>1.59 ± 0.21&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HMG-CoA synthase</td>
<td>1.0</td>
<td>1.35 ± 0.55</td>
</tr>
<tr>
<td>ApoE</td>
<td>1.0</td>
<td>1.01 ± 0.51</td>
</tr>
<tr>
<td>ABCA1</td>
<td>1.0</td>
<td>1.48 ± 0.32</td>
</tr>
<tr>
<td>LDL receptor</td>
<td>1.0</td>
<td>N.D.</td>
</tr>
<tr>
<td>CYP46A1</td>
<td>1.0</td>
<td>0.97 ± 0.34</td>
</tr>
</tbody>
</table>

<sup>a</sup> N.D., not determined.

<sup>b</sup> $p < 0.05$.

<sup>c</sup> $p < 0.01$.

<sup>d</sup> $p < 0.001$ compared with controls.

<sup>e</sup> $p < 0.05$ compared with simvastatin.
ABCA1 mRNA expression levels increased due to pravastatin treatment. In serum, pravastatin treatment caused a reduction of lathosterol concentrations of 25% \((p = 0.044)\) compared with untreated animals (controls). Liver HMG-CoA reductase mRNA expression levels \((+256\%; p < 0.001)\) and HMG-CoA synthease mRNA expression levels \((+186\%; p < 0.001)\) were significantly increased after pravastatin treatment. The expression of LDL receptor mRNA in the liver was significantly increased under pravastatin compared with controls \((+43\%; p = 0.007)\) and simvastatin \((p = 0.045)\). The ABCA1 mRNA expression levels increased due to pravastatin treatment \((+58\%; p < 0.001)\). The absolute levels of 24S-OH-Chol remained unchanged in the liver, but its ratio to cholesterol was significantly higher compared with that in simvastatin-treated animals \((p = 0.028)\).

Correlation analysis revealed a significant correlation between LDL receptor and HMG-CoAR expression in the liver of the pravastatin group \((r = 0.821; p = 0.045)\). Control animals showed a significant correlation between mRNA levels of HMG-CoAR and HMG-CoA synthase \((r = 0.739; p = 0.009)\) as well as between HMG-CoA synthase and LDL receptor \((r = 0.781; p = 0.005)\). In the control group, there was a high correlation between liver and brain ApoE mRNA \((r = 0.878; p < 0.001)\).

**Discussion**

Short-term, high-dose oral administration of simvastatin clearly affects brain cholesterol synthesis in male C57/BL6 mice as evaluated by decreased levels of the cholesterol precursor lathosterol and increased mRNA expression ratios of HMG-CoAR in whole-brain homogenates. In contrast, pravastatin failed to show an inhibitory effect on cholesterol synthesis in the brain.

There are several studies indicating that simvastatin but not pravastatin is able to penetrate the BBB (de Vries and Cohen, 1993; Saheki et al., 1994), causing CNS side effects such as sleep disturbances. The ability to cross the BBB is thought to be caused by the difference in lipophilicity.

The active forms of simvastatin and pravastatin have similar chemical structures, but pravastatin is approximately 100 times less lipophilic than simvastatin (Serajuddin et al., 1991). In theory, pravastatin should therefore be regarded as being unable to cross the BBB to a significant extent (Guillot et al., 2004). Assuming a local effect of statins, we have to consider that altering cholesterol levels in the brain might have hazardous consequences for the important role of cholesterol in neuronal growth and signal transduction. In those studies that show a gross change in cholesterol content in the brain, a serious toxic effect, resulting in demyelination, could have occurred.

In this study, significant effects on the cholesterol precursor lathosterol in the brain were observed as a result of simvastatin treatment. It is noteworthy, that in cells and organs, concentrations of cholesterol precursors and cholesterol itself differ with a factor of 1000. However, the changes in precursor levels as presented in this study reflect the potency of simvastatin to alter brain cholesterol synthesis. The pool of cholesterol in the whole brain seems to remain stable, and brain cholesterol homeostasis seems to be well regulated, ensuring the demand for cholesterol supply in this organ.

The inhibitory effects on cholesterol synthesis in the brain due to simvastatin treatment were accompanied by a compensatory increase in HMG-CoAR mRNA expression as well as an increased level of ABCA1 mRNA. Levels of ApoE mRNA were not affected.

In a previous study, high-dose treatment of transgenic PSAPP mice with atorvastatin decreased ApoE levels in the brain (Petanceska et al., 2003). However, in the present
study, ApoE mRNA levels were not affected by either of the two statins. This might be due to the short duration of treatment in our study, the different mouse strain, the genetic background, or the statins used in these experiments. However, the expression of mRNA is not necessarily correlated to protein abundance levels or enzyme activity (Gygi et al., 1999). Neither expression ratios of CYP46A1 mRNA nor levels of 24S-OH-Chol were significantly affected by the treatment, indicating that the inhibition of cholesterol synthesis had no effect on the most important mechanism for elimination of cholesterol from the brain. In a previous study in which guinea pigs were treated with the two statins, a slight but significant effect on brain levels of 24S-OH-Chol was observed (Lütjohann et al., 2004). This discrepancy between the guinea pig experiment and our study may possibly be due to the different treatment periods. In mice, however, the metabolism of this oxysterol is different. Whereas in mice, only approximately 50% of circulating 24S-OH-Chol originates from the brain (Meaney et al., 2000), in humans 24S-OH-Chol is exclusively of brain origin (Björkhem et al., 1999).

Thus, comparing results of studies on cholesterol metabolism from mice, guinea pigs, and humans has limitations. For instance, in wild-type mice, plasma levels of cholesterol are relatively low, and cholesterol is predominantly found in the high-density lipoprotein fraction (Terpstra et al., 1982), whereas in humans, most cholesterol is located in the LDL fraction (Fielding and Fielding, 1982).

Further differences between human and murine models are supported by our finding that there was no change of absolute cholesterol levels in serum and liver due to high-dose statin treatment, which is in accordance with previous reports (Endo et al., 1979; Kita et al., 1980; Dietschy and Turley, 2002). Nevertheless, other studies report slight reductions in serum/plasma cholesterol levels in mice under statin treatment (Petanceska et al., 2002; Park et al., 2003). This might be explained by the short-term treatment performed in our study.

In the liver, the levels of pravastatin were found to be markedly higher than levels of simvastatin. This finding cannot solely be attributed to the doubling of the dose. The high levels of pravastatin in the liver may be related to the fact that this specific statin is subjected to an extensive metabolism and lipophilicity, as well as the different uptake and tissue selectivity (Ziegler and Hummel-siep, 1993; van Vliet et al., 1995).

We have shown conclusively that high doses of simvastatin affect brain cholesterol synthesis in mice and that this effect is most likely the result of a direct passage of the drug across the BBB and a local inhibition of cholesterol synthesis in the brain. A stronger decrease of lathosterol concentrations in the liver. Total simvastatin concentrations in brain, liver, and serum correlated significantly whereas there was no such effect seen in pravastatin-treated animals. The different effects of simvastatin and pravastatin on cerebral and peripheral cholesterol synthesis may in part be due to the differences in metabolism and lipophilicity, as well as the different uptake and tissue selectivity (Ziegler and Hummelsiep, 1993; van Vliet et al., 1995).

Acknowledgments

We are grateful to Sankyo, Inc. for supplying us with pravastatin.

References


Gygi SP, Franza BR, and Aebersold R (1999) Correlation between protein abundance levels or enzyme activity (Gygi et al., 1999). Neither expression ratios of CYP46A1 mRNA nor levels of 24S-OH-Chol were significantly increased by both statins, with more marked effects for pravastatin than for simvastatin. In the mouse, ApoE mRNA levels were not affected by either of the two statins. This might be due to the short duration of treatment in our study, the different mouse strain, the genetic background, or the statins used in these experiments. However, the expression of mRNA is not necessarily correlated to protein abundance levels or enzyme activity (Gygi et al., 1999). Neither expression ratios of CYP46A1 mRNA nor levels of 24S-OH-Chol were significantly affected by the treatment, indicating that the inhibition of cholesterol synthesis had no effect on the most important mechanism for elimination of cholesterol from the brain. In a previous study in which guinea pigs were treated with the two statins, a slight but significant effect on brain levels of 24S-OH-Chol was observed (Lütjohann et al., 2004). This discrepancy between the guinea pig experiment and our study may possibly be due to the different treatment periods. In mice, however, the metabolism of this oxysterol is different. Whereas in mice, only approximately 50% of circulating 24S-OH-Chol originates from the brain (Meaney et al., 2000), in humans 24S-OH-Chol is exclusively of brain origin (Björkhem et al., 1999).

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