Simvastatin Protects against Multiple Low-Dose Streptozotocin-Induced Type 1 Diabetes in CD-1 Mice and Recurrence of Disease in Nonobese Diabetic Mice

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ABSTRACT

Statins are drugs well known for their cholesterol-lowering properties. Lately, statins have been shown to possess anti-inflammatory properties that might be attributed to inhibition of leukocyte adhesion and migration to sites of inflammation. Therefore, we have explored the effects of administration of simvastatin (30 mg/kg body weight given i.p. once a day, from days 4–14) on the development of diabetes induced by multiple low-dose streptozotocin (MLDS) in CD-1 mice, a type 1 diabetes model. We found that treatment with simvastatin could delay and in certain mice fully protect against MLDS-induced diabetes. The protective effect could last up to 3 weeks after simvastatin treatment was ended. Morphological examinations of the pancreas suggest that simvastatin might reduce the islet inflammation. Based on experiments in vitro, using isolated pancreatic islets, we conclude that the protective effect of simvastatin is not mediated by a direct effect on streptozotocin action but rather the result of an immunomodulatory effect. This was reinforced by the finding that simvastatin treatment also prolonged islet function in the recurrence of disease model in diabetic nonobese diabetic mice.

Simvastatin (for chemical structure, see Weitz-Schmidt, 2002) belongs to the statin family, a class of drugs that competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step of the cholesterol synthesis pathway. Statins are frequently prescribed to prevent coronary heart disease and have been shown to exert this action even without a significant drop in blood cholesterol levels, suggesting anti-inflammatory properties independent of its cholesterol-lowering effects (Downs et al., 1998; Ridker et al., 1998; Weitz-Schmidt, 2002).

Mevalonate is a precursor not only for cholesterol but also for isoprenoids, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These are necessary for the post-translational lipid modification of a variety of proteins belonging to the small GTP binding proteins, e.g., Ras, Rho, and Rab (Weitz-Schmidt, 2002). Statins might therefore prevent the membrane localization and function of these proteins by inhibiting HMG-CoA reductase. There is strong evidence that these effects of statins, at least in part, are the basis for its anti-inflammatory properties. For example, Liu et al. (1999) have shown that inhibition of integrin activation by statins correlates with the reduced geranylgeranylation of Rho, and Takeuchi et al. (2000) have shown that statins prevent intercellular adhesion molecule 1 (ICAM-1) expression in endothelial cells by blocking Rho activation.

Some statins, including simvastatin, have also been shown to bind to an allosteric site of the integrin leukocyte function-associated antigen-1 (LFA-1), locking LFA-1 in its inactive form, thereby preventing LFA-1-mediated adhesion and co-stimulation of lymphocytes (Weitz-Schmidt et al., 2001). In addition, simvastatin has recently been shown to markedly inhibit both developing and a clinically evident collagen-induced arthritis, a Th1-driven model of murine inflammatory arthritis (Leung et al., 2003).

Type 1 diabetes is considered to be an autoimmune disease characterized by the infiltration of T-cells and macrophages in and around islets of Langerhans (insulitis) with concomitant selective destruction of insulin producing β-cells. These mononuclear cells may cause this destruction either directly or through the secretion of proinflammatory cytokines, such as...
as interleukin-1β and interferon-γ, and free radicals (Bach, 1995; Sandler et al., 2000).

In light of the findings referred to above, we have studied the effect of simvastatin on the development of hyperglycemia and insulitis induced by injections of multiple low-dose streptozotocin (MLDS) in CD-1 mice. In this diabetes model, shown to be T-lymphocyte dependent (Paik et al., 1980; Herold et al., 1992; Sandler et al., 2000), the mice receive five daily i.p. injections of streptozotocin (STZ), and a progression of hyperglycemia and insulitis evolve during a 2-week period.

We have also studied the effect of simvastatin on the recurrence of disease (ROD) model in nonobese diabetic (NOD) mice. In this model, syngeneic pancreatic islets from young healthy male mice are transplanted to spontaneously diabetic female NOD mice. If the transplantation is successful, these mice become normoglycemic within 1 to 2 days. The grafted islets are subsequently destroyed by a recurrent autoimmune process (recurrence of disease) but not by graft rejection (Nomikos et al., 1986; Sandberg et al., 1997; Panerai et al., 2001). Recurrence of hyperglycemia usually occurs within 6 to 8 days.

Materials and Methods

Reagents

Collagenase A was obtained from Boehringer Mannheim (Mannheim, Germany). RPMI 1640 culture medium, fetal calf serum (FCS), and STZ were supplied by Sigma Chemicals (St. Louis, MO). Simvastatin was purchased from Sigma-Aldrich Sweden AB (Stockholm, Sweden) and later kindly provided by Merck Research Laboratories (Rahway, NJ), and bovine serum albumin (BSA) was purchased from ICN Biomedicals (Aurora, IL). For the glucose-induced insulin release experiments, we used Krebs-Ringer-bicarbonate buffer + HEPES (KRBH; 114.3 mM NaCl, 4.74 mM KCl, 1.15 mM KH₂PO₄, 1.18 mM MgSO₄, 25.0 mM NaHCO₃, 10.0 mM HEPES, 4.26 mM NaOH, 2.54 mM CaCl₂, pH 7.4).

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Animals and Methods

All experiments were approved by the local animal ethics committee for Uppsala University.

MLDS. Outbred adult male CD-1 mice (Charles River, Sulzfeld, Germany), 9 to 18 weeks old and weighing between 30 and 40 g, were used. This strain of mice has earlier been shown to be susceptible to MLDS diabetes (Lilk and Rossini, 1976). The mice had free access to tap water and pelleted food and were housed in a room with a 12-h light/dark cycle.

The mice were divided into four different treatment groups: saline + vehicle, saline + simvastatin, MLDS + saline, and MLDS + simvastatin. STZ was dissolved in saline immediately before administration. Simvastatin was dissolved in 100 μl of ethanol and 150 μl of 0.1 N NaOH, incubated at 50°C for 2 h, and then pH was adjusted to 7 and volume corrected to 1 ml [adapted from a study by Leung et al. (2003) on experimental arthritis in mice]. Once a day, for 5 consecutive days, the mice received an i.p. injection of either saline (0.2 ml) or freshly prepared STZ (40 mg/kg body weight; 0.2 ml) dissolved in saline. From day 4, the mice received daily i.p. injections of either vehicle (0.2 ml) or simvastatin (30 mg/kg body weight; 0.2 ml) dissolved in vehicle. This treatment was maintained until day 14. On days 4 and 5, the STZ/saline injections were administered 30 min before the simvastatin/vehicle injections.

The mice were killed for morphologic examination of the pancreatic glands, either on day 14 or 35. Blood samples were taken from the tail tip of nonfasting mice for blood glucose determination, with a blood glucose meter (Medisense, London, UK), on day 0 before any injections and on days 3, 7, 10, 14, 17, 21, 24, 28, 31, and 35. The mice were considered hyperglycemic with a blood glucose concentration \( \geq 11.1 \text{ mM} \). The mice were weighed on days 0, 7, 14, and 35.

The mice of the MLDS study were killed by cervical dislocation, and the pancreatic glands were removed, fixed in 10% formalin for 24 h, embedded in paraffin, and cut into 5-μm-thin sections. The sections were stained with hematoxylin and eosin and examined under a microscope. The pancreatic islet histology was ranked into four arbitrary classes, where class A denotes normal islet structure; class B, mononuclear cell infiltration in the peri-insular area; class C, heavy mononuclear cell infiltration into a majority of islets (i.e., insulitis); and class D, only a few residual islets present, often showing an altered architecture and pyknotic cell nuclei (Sandler and Andersson, 1985). The examiner was unaware of the origins of the sections.

ROD. The NOD mice were originally obtained from the Clea Company (Aobadai, Japan) and subsequently inbred under pathogen-free conditions at the Animal Department (BMC, Uppsala, Sweden).

Pancreatic islets were isolated (as described below) and precultured for 3 to 5 days, after which 600 pancreatic islets from healthy male NOD mice were transplanted under the left kidney capsule to newly diabetic female NOD mice. Islet recipients were anesthetized with an i.p. injection of Avertin [a 2.5% (v/v) solution of 10 g of 97% 2,2,2-tribromo-ethanol in 10 ml of 2-methyl-2-butanol; Kemila, Stockholm, Sweden]. Starting on day 0, before the transplantation, and then once per day, the mice received an i.p. injection with either vehicle (0.2 ml) or simvastatin (30 mg/kg body weight; 0.2 ml) dissolved in vehicle. The treatment was maintained until recurrence of disease, i.e., until the mice had a blood glucose value \( \geq 11.1 \text{ mM} \) for 2 consecutive days, after which the mice were killed. Blood samples were taken and blood glucose determined as described above, on day 0, before transplantation or any injections, and then once a day until the end of treatment.

Islet Exposure to STZ in Vitro

After a 6- to 7-day-long preculture, islets from CD-1 mice were subsequently divided into groups of 35 and transferred to culture dishes containing 1 ml of sterile KRBH supplemented with 5.6 mM glucose and 2 mg/ml BSA. The islets were first incubated for 30 min with or without simvastatin (60 or 600 mg/l) and then for another 30 min with saline or STZ dissolved in saline (final concentration, 1.8 mM). After rinsing and removal of the medium, the islets were cultured overnight in RPMI 1640 supplemented with 10% FCS (v/v) and antibiotics, with medium changes every 2nd day. All islet cultures and incubations were kept at 37°C in humidified air + 5% CO₂ in this study.

Islet Glucose-Induced Insulin Release and Insulin Content

To determine the glucose-induced insulin release, triplicate groups of 10 islets were transferred to 100 μl of KRBH, supplemented with 2 mg/ml BSA and 1.7 mM glucose, and incubated for 1 h. The islets were then transferred to 100 μl of KRBH, supplemented with 2 mg/ml BSA and 16.7 mM glucose, and incubated for another 1 h. The incubation medium was then collected for insulin concentration determinations. To analyze the insulin contents of these islets, the islets were pooled in groups of 30 and ultrasonically disrupted in 200 μl of redistilled water. A 50-μl volume of the homogenate was then mixed with 125 μl of acid ethanol [0.18 M HCl
in 96% (v/v) ethanol, and insulin was extracted at 4°C overnight before determination. All insulin concentration determinations were performed with a high-range rat insulin enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden).

Statistical Analysis

Data are presented as means ± S.E.M. In the MLDS experiments, groups of data were compared by one-way ANOVA, with subsequent pairwise comparison procedures by Student-Newman-Keuls method. In the ROD experiments, the days of recurrent hyperglycemia were compared by Students t test. We also used Fisher’s exact test to compare the proportion of hyperglycemic mice in different experimental groups. In the in vitro experiments, groups of data were compared by one-way repeated measurement ANOVA, with subsequent all pairwise comparison procedures by Student-Newman-Keuls method. A p value of less than 0.05 was considered statistically significant. In the glucose-induced insulin release experiments, where islets were incubated in triplicates, a mean was calculated for each experimental group and considered as one separate observation. Statistical analysis was performed using SigmaStat (SPSS Inc., Chicago, IL).

Results

Effects of Simvastatin on MLDS-Induced Hyperglycemia and Insulitis. Mice treated with MLDS + vehicle showed an increase in mean blood glucose concentrations, from day 10 onwards, compared with both control-treated mice (saline + vehicle) and mice treated with MLDS + simvastatin (Fig. 1). All mice treated with MLDS + vehicle were hyperglycemic (blood glucose ≥ 11.1 mM) on day 14 (Table 1). The mice treated with MLDS + simvastatin showed a delayed onset of hyperglycemia, with a significant increase in mean blood glucose concentration, compared with control, on day 14 (Fig. 1). At this time point, 5 of 14 mice were still considered normoglycemic (blood glucose < 11.1 mM), and the proportion of hyperglycemic mice was significantly less compared with the MLDS + vehicle group, when compared with Fisher’s exact test (Table 1). Both control mice treated with saline + vehicle and mice treated with saline + simvastatin remained normoglycemic throughout the study. Morphologic examination of the pancreas on day 14 revealed that, of the six mice receiving MLDS + saline, four were ranked C (i.e., showed marked insulitis), and two were ranked B (i.e., showed peri-insular mononuclear infiltration) (Table 2). In the MLDS + simvastatin group, two of the mice were ranked A (i.e., normal islet structure and no signs of inflammation), four mice were ranked B, and another two were ranked C (Table 2). The mice receiving saline + vehicle or saline + simvastatin were all ranked A (Table 2).

In a separate experimental series, mice were killed on day 35, i.e., 21 days after simvastatin or vehicle treatment had been stopped. Thus, the mice treated with MLDS + vehicle showed an increase in mean blood glucose concentrations, from day 14 onwards, compared with control-treated mice (Fig. 2). The mice treated with MLDS + simvastatin showed increased mean blood glucose levels, compared with control, only on days 31 and 35 (Fig. 2). Although from day 28 onwards, their mean levels were not significantly different from that of the MLDS + vehicle group (Fig. 2). However, two of the six mice in the MLDS + simvastatin group were still normoglycemic at day 35 (data not shown).

Morphologic examination of the pancreas on day 35 shows that of the six mice receiving MLDS + saline, five were ranked D (i.e., only a few islets present, often with an altered architecture), and one was ranked A (Table 2). In the group receiving MLDS + simvastatin treatment, three mice were ranked D and three ranked A (Table 2). The mice receiving saline + vehicle or saline + simvastatin were all ranked A (Table 2).

Administration of simvastatin did not affect body weight in

![Fig. 1. Blood glucose concentrations in mice treated with saline + vehicle (black circles), saline + simvastatin (white circles), MLDS + vehicle (black triangles), or MLDS + simvastatin (white triangles). STZ (40 mg/kg body weight) or saline was administered as i.p. injections, once a day, for 5 consecutive days, starting on day 1. Simvastatin (30 mg/kg body weight) or vehicle was administered as i.p. injections, once a day, from days 4 to 14. Values are means ± S.E.M for 10 to 14 animals. *p < 0.05 versus the group saline + vehicle; #, p < 0.05 versus the group MLDS + simvastatin, using one-way ANOVA with subsequent all pair-wise comparison procedures by Student-Newman-Keuls method.](image-url)

### Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Mice with Blood Glucose</th>
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<tr>
<td></td>
<td>Days 1–5</td>
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<tr>
<td>MLDS + Vehicle</td>
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<td>MLDS + Simvastatin</td>
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* p < 0.05 vs. the MLDS + vehicle group, using Fisher’s exact test.

### Table 2

<table>
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<tr>
<th>Treatment</th>
<th>Morphology Rank</th>
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<td>Day 14</td>
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<tr>
<td>Saline + Vehicle</td>
<td>A</td>
</tr>
<tr>
<td>Saline + Simvastatin</td>
<td>B</td>
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<tr>
<td>MLDS + Vehicle</td>
<td>C</td>
</tr>
<tr>
<td>MLDS + Simvastatin</td>
<td>D</td>
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<tr>
<td>Day 35</td>
<td></td>
</tr>
<tr>
<td>Saline + Vehicle</td>
<td>A</td>
</tr>
<tr>
<td>Saline + Simvastatin</td>
<td>B</td>
</tr>
<tr>
<td>MLDS + Vehicle</td>
<td>C</td>
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<tr>
<td>MLDS + Simvastatin</td>
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In the ROD experiments, the days of recurrent hyperglycemia were compared by pairwise comparison procedures by Student-Newman-Keuls method. We also used Fisher’s exact test to compare the proportion of hyperglycemic mice in different experimental groups. In the in vitro experiments, groups of data were compared by one-way repeated measurement ANOVA, with subsequent all pairwise comparison procedures by Student-Newman-Keuls method. A p value of less than 0.05 was considered statistically significant. In the glucose-induced insulin release experiments, where islets were incubated in triplicates, a mean was calculated for each experimental group and considered as one separate observation. Statistical analysis was performed using SigmaStat (SPSS Inc., Chicago, IL).
any of the experiments. Mice treated with saline + vehicle increased in weight during the treatment period (day 0, 34.1 g; day 14, 35.6 g (p = 0.037; n = 7)) and so did mice treated with saline + simvastatin (day 0, 32.4 g; day 14, 33.7 g (p = 0.003; n = 7)). Mice treated with MLDS + vehicle did not increase in weight (day 0, 34.3 g; day 14, 34.8 g (p = 0.352; n = 9)) and also mice treated with MLDS + simvastatin failed to increase in weight (day 0, 33.4 g; day 14, 34.3 g (p = 0.147; n = 10)).

**Effects of Simvastatin on Islet Dysfunction, Induced by STZ, in Vitro.** The pancreatic islets in this experiment were incubated for 30 min, at 5.6 mM glucose, in the presence or absence of simvastatin, used in two different concentrations (60 or 600 mg/l), and then incubated for another 30 min with or without the addition of 1.8 mM STZ. After this incubation, the islets were cultured overnight in fresh culture medium before they were analyzed for their glucose-induced insulin release.

The insulin secretion at 1.7 mM glucose was increased from islets incubated with STZ alone, and this was not seen with the high concentration of simvastatin (Fig. 3A). The two different concentrations of simvastatin alone did not affect secretion at this glucose concentration. At 16.7 mM glucose, simvastatin alone did not affect insulin release, although it tended to decline with the higher concentration of simvastatin (p = 0.078) (Fig. 3A). Moreover, at 16.7 mM glucose, the insulin secretion was decreased both with STZ alone and with the addition of the high concentration of simvastatin, whereas the lower simvastatin appeared to partly counteract STZ-induced depression (Fig. 3A). However, when calculating the relative stimulation [i.e., the quota of the insulin secretion at the two different glucose concentrations (16.7 mM/1.7 mM)], all treatment groups were lowered compared with that of control (Fig. 3A). The analyzed insulin contents of the islets, extracted after the glucose-induced insulin release experiments, showed a decrease in islets treated with the high concentration of simvastatin alone and in islets treated with STZ with or without the different concentrations of simvastatin (Fig. 3B).

**Effects of Simvastatin on ROD in NOD Mice.** The mice treated with simvastatin showed a delayed onset of ROD, with a mean value of 13.1 ± 2.6 days compared with 13.6 ± 0.5 days in mice treated with vehicle (p = 0.042, n = 8 in both groups). On day 7 of the study, five of eight vehicle-treated mice had developed diabetes again compared with none (zero of eight) of the simvastatin-treated mice (p = 0.026 when compared with Fisher's exact test) (Fig. 4). On day 10, all (eight of eight) vehicle-treated mice were diabetic, but only four of eight mice treated with simvastatin were diabetic (p = 0.077 compared with Fisher's exact test) (Fig. 4). In the simvastatin group, the last mouse becoming hyperglycemic reverted on day 29.

**Discussion**

One of the aims of this study was to examine whether administration of simvastatin could affect immune-mediated
MLDS-induced hyperglycemia and insulitis in CD-1 mice. Indeed, our results show that simvastatin could partly counteract the rise in blood glucose seen after MLDS treatment. Simvastatin was given on days 4 to 14, and with this regimen, the blood glucose levels of the animals remained lower than the mice given vehicle + MLDS in the 2-week study (Fig. 1). In fact, among the individual mice on day 14, we observed that 5 of 14 mice treated with MLDS + simvastatin were still clearly normoglycemic (<8.8 mM), whereas all mice (12 of 12) treated with MLDS + vehicle were hyperglycemic on this day. Moreover, on day 14, mice treated with MLDS + simvastatin showed a tendency toward reduced mononuclear cell infiltration in their pancreatic islets, compared with mice treated with MLDS + vehicle.

Next, we investigated whether the protective effect of simvastatin could be maintained when simvastatin administration was discontinued. For this purpose, the mice were followed for another 3 weeks after day 14. In this experiment, the protective effect of simvastatin lasted until day 28, as evidenced by the mean blood glucose levels of the mice. It should be noted that still on day 35, two mice were normoglycemic at the end of the experiment (not shown), and when the pancreatic morphology was examined, three mice showed a normal appearance with no signs of inflammation (Table 2).

Our experiments in vitro show that exposure of mouse pancreatic islets to different concentrations of simvastatin (60 and 600 mg/l) could not prevent inhibition of islet glucose-induced insulin release following a high concentration of STZ (1.8 mM). One might argue that the low concentration of simvastatin seemed to partly prevent the effects of STZ on insulin release at 16.7 mM glucose, but this was apparently due to leakage of insulin from damaged β-cells in the islets (Fig. 3A). This interpretation is corroborated by the markedly reduced ratio of relative stimulation of insulin release. Moreover, when we examined the islets under a stereomicroscope after exposure to simvastatin ± STZ, it was clear that simvastatin itself caused a dose-dependent destruction of the islets. These effects were more pronounced when STZ and simvastatin was combined. This is in line with the decreased islet insulin contents in these experimental groups (Fig. 3B).

The possible toxic effect by simvastatin to the pancreatic islets seen in vitro was not evident in vivo, with the protocols used in the MLDS or ROD model. On the other hand, in pilot experiments with the MLDS model, we used a different protocol adopted from a study in a rheumatoid arthritis model by Leung et al. (2003) in which the concentration of simvastatin was 40 mg/kg body weight and administered from days 1 until 14. However, this protocol seemed not to be feasible in that about one of three of the animals treated displayed swollen abdomens, and when killed, adhesions between intestines were observed. Therefore, we modified the protocol to that presented herein, and then we did not find any signs of toxicity. It is likely the CD-1 mice are more sensitive to simvastatin than the DBA/1 mice used by Leung et al. (2003).

The results from our study show that simvastatin can counteract hyperglycemia in two murine models of type 1 diabetes. There might be differences among various statins in their capacity to affect hyperglycemia in type 1 diabetes mouse models. Thus, oral or i.p. administration of atorvastatin to C57BL/6 mice given STZ 60 mg/kg body weight and administered from days 1 until 14 did not prevent hyperglycemia (Palomer et al., 2005). It should be noted that these authors used an unconventional MLDS protocol in which direct β-cell cytotoxicity must be considered as an important factor. Oral atorvastatin was also given to NOD mice, commenced after 5 weeks of age, but this could not significantly decrease the incidence of diabetes (Palomer et al., 2005). Moreover, atorvastatin given to NOD mice orally (1–50 mg/kg body weight) from 6 to 12 weeks of age could not affect the prevalence of diabetes (Lozanoska-Ocher et al., 2006). In the latter study, atorvastatin, however, reduced the number of β-cell pathogenic CD8 T-cells.

Lately, statins have been shown to possess both HMG-CoA-reductase-dependent and -independent anti-inflammatory effects by which they might affect leukocyte adhesion and migration to sites of inflammation as well as leukocyte costimulation (Weitz-Schmidt, 2002). For example, statins have been shown to inhibit chemokine (monocyte chemotactic protein-1) expression in activated leukocytes, to block integrin (very late antigen 4 and LFA-1) expression and...
activation in leukocytes, and to decrease adhesion molecule (ICAM-1) expression on monocytes and in stimulated endothelial cells (Niwa et al., 1996; Romano et al., 2000; Takeuchi et al., 2000; Yoshida et al., 2001). Of these, ICAM-1 and LFA-1 have been shown to be expressed in pancreatic islets with a peri-insular infiltration of mononuclear cells as well as in islets with an intraislet infiltration in NOD mice (Martin et al., 1996). Based on these findings, we suggest that the protective effect of simvastatin observed presently in the MLDS and ROD model of type 1 diabetes is probably related to the anti-inflammatory actions described above. It cannot, however, be excluded that the protective action of simvastatin observed herein is a specific action by the drug and not necessarily an action by simvastatin as belonging to the class of statins.

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References


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