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*Parts of this chapter have been published in: Arthritis & Rheumatism 2002 Oct 46(10):2794-803*
Lack of isoprenoid products raises ex vivo interleukin-1β secretion in the HyperImmunoglobulinemia D periodic fever syndrome

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Abstract

Objective
To investigate whether the increased interleukin (IL)-1β and IFN-γ secretion in hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is due to the accumulation of mevalonate, the substrate of the deficient enzyme mevalonate kinase (MK), or the lack of its products, the isoprenoid compounds.

Methods
The effects of lovastatin and farnesol (FOH), geraniol (GOH), geranylgeraniol (GGOH), and mevalonate on peripheral blood mononuclear cells (PBMCs) from 8 patients with MK deficiency and from 13 controls were studied. Lovastatin inhibits isoprenoid biosynthesis by reducing the production of mevalonate. FOH, GOH and GGOH restore isoprenoid biosynthesis downstream from MK. Culture supernatants were collected for cytokine analysis 48 hours after stimulation with monoclonal antibodies against CD2 + CD28.

Results
Lovastatin induced a 15-fold rise in IL-1β secretion by normal anti-CD2 + CD28-stimulated cells. This effect could be countered by mevalonate and, to a lesser extent, by FOH, GOH and GGOH. In the absence of lovastatin, mevalonate did not change IL-1β and IFN-γ secretion. Stimulated MK-deficient cells secreted 9-fold more IL-1β and up to 4-fold more IFN-γ than control PBMCs, rising further in the presence of lovastatin. The effect of lovastatin on IL-1β and IFN-γ secretion was reduced by mevalonate, FOH, and GGOH. Isoprenoid biosynthesis in PBMCs from patients was impaired due to the endogenous MK deficiency. Bypassing this defect with FOH and GGOH, in the absence of lovastatin, led to a marked reduction in IL-1β and IFN-γ secretion by these cells.

Conclusion
In this model, shortage of isoprenoid end products contributes to increased IL-1β and IFN-γ secretion by MK-deficient PBMCs, whereas excess mevalonate does not.

Introduction
Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), also known as Dutch type periodic fever (MIM#260920), is an autosomal recessive disorder, characterized by febrile attacks recurring at more or less regular intervals and the
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presence of an elevated serum IgD concentration (>100 IU/ml)(1). More than 170 patients have been diagnosed with the disease worldwide (2). Clinical features during the febrile attacks include cervical lymphadenopathy, splenomegaly, hepatomegaly, skin rash, oral ulcers, vomiting, diarrhea, arthralgias, and arthritis. Patients often report malaise, chills, headache, nausea or abdominal pain (1). During these febrile crises, blood tests reflect an acute inflammatory state, with leukocytosis and elevated acute phase reactants including C reactive protein. Serum levels of pro-inflammatory cytokines, such as interleukin (IL)-6, and interferon-γ (IFN-γ), rise during fever attacks (3;4). Also, between attacks, isolated peripheral blood mononuclear cells (PBMCs) from HIDS patients secrete large amounts of proinflammatory cytokines, such as IL-1β (5). However, what causes the rise in production of these cytokines has remained unclear.

In 1999, the underlying genetic defect of the syndrome was identified, namely, mutations in the gene MVK, which lead to a deficiency of the enzyme mevalonate kinase (MK) (6;7). Mutations in the same gene are responsible for mevalonic aciduria (MA, MIM#251170), a syndrome with episodic fever, mental retardation and dysmorphic features (8;9). MK catalyzes the phosphorylation of mevalonic acid into 5-phosphomevalonate and is the enzyme immediately following 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase in the isoprenoid biosynthesis pathway (10)(figure 1). This pathway produces cholesterol, which, in turn, is a precursor for bile acids and steroid hormones. Furthermore, this biosynthetic route yields a number of non-sterol isoprenoids. The latter are hydrophobic molecules, such as dolichol and the polyisoprene side chains of heme-A and ubiquinone. Non sterol isoprenoids play a vital role in the prenylation of certain proteins. In this process hydrophobic polyisoprene moieties are covalently attached to specific target proteins. Prenylation comes in two forms, the attachment of farnesyl groups (from farnesylpyrophosphate (FPP)) or of geranylgeranyl groups (from geranylgeranylpyrophosphate (GGPP)).

In HIDS, the deficiency of MK causes accumulation in plasma of its substrate, mevalonic acid, which is then excreted in the urine (7). The causal link between MK deficiency and inflammation remains to be clarified. Inflammation has to result from either the excess of mevalonic acid or the shortage of one or more products of isoprenoid biosynthesis.

Recently, it has become apparent that impairment of isoprenoid biosynthesis can indeed influence immune function. In vitro, inhibitors of HMG-CoA reductase, also known as statins, may either suppress or enhance inflammatory responses, depending on the cell type studied and the way in which these cells were stimulated. Many anti-inflammatory effects of statins have been reported, including the reduction of lymphocyte proliferation, and of the expression of major histocompatibility complex class II molecules, matrix metalloproteinases, cytokines, and chemokines (11-15). Also, these compounds do have pro-inflammatory properties. Statins enhance endothelial expression of cellular adhesion molecules (16). Interestingly, the secretion of IL-1β, IFN-γ and IL-18 by PBMCs stimulated ex vivo with inactivated M.tuberculosis is augmented greatly by the inhibition of isoprenoid biosynthesis with statins (17). The increased cytokine secretion appeared to be Th1 induced and to be due to lack of isoprenoids, since addition of mevalonic acid reduced cytokine secretion to control levels.

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The question is whether the reported increased secretion of pro-inflammatory cytokines in HIDS could be explained along similar lines. If lack of isoprenoids were responsible, then the addition of isoprenoid intermediary metabolites to cells from HIDS patients should correct the cytokine hypersecretion. To be effective, these compounds should enter the isoprenoid pathway downstream from the metabolic block in HIDS, i.e. MK. FPP, geranyl pyrophosphate (GPP) and GGPP are such intermediary metabolites. Entry in living cells is impaired, however, by the presence of hydrophilic pyrophosphate groups. The fatty alcohols farnesol (FOH), geraniol (GOH) and geranylgeraniol (GGOH) are hydrophobic molecules that enter living cells freely and, once inside, are converted into FPP, GPP and GGPP by two successive monophosphorylations (18).

Therefore we studied the effects of FOH, GOH, GGOH and mevalonate in the presence or absence of lovastatin on the IL-1β secretion by PBMCs.

Figure 1. The isoprenoid biosynthesis pathway.
Schematic overview of the isoprenoid biosynthesis pathway, indicating the MK deficiency in HIDS and MA, the inhibition of HMG-CoA reductase by lovastatin and the point of entry of FOH, GOH and GGOH.
Patients and methods

Cell culture
Pediatric HIDS or MA patients visiting our outpatient clinic for regular follow-up were approached to participate in the study. After approval by the Ethical Review Board and written informed consent by the patients’ parents, blood was drawn by venipuncture in sterile pyrogen-free heparinized plastic tubes. All patients were free of symptoms and were not taking antiinflammatory drugs at the time of blood sampling. Healthy adult volunteers served as controls. PBMCs were isolated by Ficoll density gradient centrifugation (Amersham Pharmacia Biotech, Uppsala, Sweden). We incubated 1 x 10^5 cells per well in 96-well-flat-bottom microtiter plates in RPMI 1640 (Life Technologies, Grand Island, NY) supplemented with 5 % heat inactivated fetal calf serum (Life Technologies, Grand Island, NY) filtrated through a 0.2 µm filter, 2 mmol/L L-glutamine and 1% penicillin-streptomycin. Incubations were performed in quadruplicate at 37 °C in a humidified atmosphere containing 5 % CO_2 in air. The cultures were performed in the presence or absence of lovastatin (final concentration 5 µM). In addition, either 1 mM mevalonate, 10 µM farnesol (FOH), 10 µM geraniol (GOH), 10 µM geranylgeraniol (GGOH) or medium was added at the start of the experiments. Lovastatin, mevalonic acid, FOH, GOH, and GGOH were purchased from Sigma (St. Louis, MO). Both lovastatin, dissolved in ethanol, and mevalonic acid lactone were converted to lovastatin and mevalonate, respectively, by hydrolyzation (0.1M NaOH), followed by neutralization and stabilization at pH 7.4 with 0.05 M HEPES and HCl (0.1 M).

After 18 hours incubation either *Mycobacterium tuberculosis*, Purified Protein Derivative (PPD) of *M.tuberculosis* (Statens Serum Institut, Copenhagen, Denmark), mycobacterial heat shock protein HSP60 (Sanbio, San Diego, CA), anti-CD2 + anti-CD28 (PeliCluster CD 2.1, CD 2.2 and CD 28, CLB Amsterdam, The Netherlands) or medium was added to the cultures without any other change in the medium. The incubations were continued for an additional 48 hours. At the end of the incubations supernatants were aspirated and stored at -20 °C until analysis.

Cytokine measurements
Cytokine concentrations were measured in thawed samples, using commercially available enzyme-linked immunosorbent assays (PeliKine-compact™ human IFN-γ, IL-1β, IL-6 and TNF-α ELISA kits CLB Amsterdam, The Netherlands). The assays were performed according to the manufacturer’s instructions, and all samples were tested in duplicate.

Lymphocyte proliferation
PBMCs at a concentration of 1 x 10^5 PBMC/well were cultured in 96-well, flat-bottomed microtiter plates under the conditions as described above. After 48 hours of incubation, cells were pulse-labeled with 1 µCi ³H-labeled thymidine for 18 hours at 37 °C. Cells were harvested and incorporation of ³H-labeled thymidine was measured in a liquid scintillation counter. Results were shown as average counts per minute (cpm) of quadruplicate cultures.
Statistical analysis
Cytokine production under different conditions was compared using Wilcoxon’s signed rank test. P values (2-tailed) less than 0.05 were considered significant. Lymphocyte proliferation was similarly analyzed. All analyses were performed using GraphPad Prism 3.0 software (GraphPad Software, San Diego, CA). Values are expressed as the mean ± SD.

Results

Patients
Seven HIDS patients participated in the study. In a previous study, they had been described as patients 119, 132, 135, 137, 139, 142, and 192 (19). In all patients, MK deficiency had been established and mutations had been identified in both alleles of their MVK genes. Two patients (a brother and sister) were homozygous for the c. 1129 G > A (V377I) mutation, 4 patients were compound heterozygous for the mutant alleles V377I and c. 803 T > C (I268T), and 1 patient carried the V377I and c. 59 A > C (H20P) alleles. The MA patient was a 2-year-old boy who presented with episodes of high-grade fever, anorexia, vomiting, and macular rash. His mental development had been adequate. His head circumference, though still normal, had grown slowly, but his weight and height gain had been excellent. He had no dysmorphic features. During febrile attacks, he showed markedly elevated acute-phase reactants and neutrophil leukocytosis. Urine mevalonic acid was extremely elevated (5,461 µmoles/m mole creatinine). MK activity in fibroblasts was 0.18 pmoles/minute/mg (0.12% of normal). He was compound heterozygous for the mutant alleles c. 1000G>A (A334T) and 421_422insG.

Figure 2. Cytokine secretion by PBMCs from normal controls incubated in the absence or presence of 5 µmol/l lovastatin. T-cell stimuli were none (Medium), M.tuberculosis (MT), PPD of M.tuberculosis (PPD), anti-CD2+CD28 (CD2/28), and mycobacterial heat shock protein (HSP 60).
A. IL-1β secretion (n=2)
B. IFN-γ secretion (n=1)

Cytokine secretion induced in normal mononuclear cells by anti-CD2+CD28 can be augmented by lovastatin
We tested the ability of several T-cell stimuli, in addition to M. tuberculosis, to induce statin-sensitive cytokine secretion (Figure 2). In the absence of lovastatin, the secretion of IL-1β was not significantly stimulated by M. tuberculosis, PPD, anti-CD2+CD28, or HSP60 (Figure 2A). However, in the presence of both lovastatin and T-cell stimuli, IL-1β secretion rose 7-fold (PPD) to 15-fold (CD2+CD28).
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IFN-γ secretion was stimulated by *M. tuberculosis*, PPD and anti-CD2+CD28 (Figure 2B). Anti-CD2+CD28 elicited the strongest response. Combination with lovastatin induced a modest further increase of IFN-γ secretion, but this did not reach significance (data shown for 1 representative control). These stimuli did not induce secretion of IL-6, nor did the secretion of IL-6 change upon incubation with lovastatin (data not shown). Since the anti-CD2 + CD28-induced IL-1β secretion was equal to or more than that induced by *M tuberculosis*, PPD, or HSP60 and since this secretion was augmented consistently by lovastatin, only anti-CD2 + CD28 was used as a stimulus in all subsequent experiments. Moreover, anti-CD2 + CD28 provides the strongest IFN-γ response in control PBMCs both in the absence as well in the presence of lovastatin.

Mononuclear cells from HIDS and MA patients produce more IL-1β and IFN-γ than control cells

Control cells secrete only small amounts of IL-1β when stimulated with CD2+CD28. PBMCs from HIDS patients excrete 9-fold more IL-1β than control cells (p<0.005). Cells from the MA patient produced even more IL-1β. HMG-CoA reductase inhibition by lovastatin caused a further elevation of IL-1β excretion by anti-CD2+CD28 activated cells from both patients (2.4-fold rise; *P* < 0.05) and controls (9.4-fold rise; *P* < 0.01) (Figure 3A). Spontaneous secretion of IL-6, known to be elevated in HIDS, was also raised in MA (17028 pg/ml vs 2260 pg/ml in controls, data not shown). IFN-γ secretion in patients tended to be higher (though not significantly) in HIDS cells than in control cells. IFN-γ secretion by MA cells exceeded that of normal controls 4-fold. Lovastatin tended to increase IFN-γ secretion by cells from most controls and HIDS patients, but not the already high concentrations of IFN-γ by PBMCs from the single MA patient (figure 3B).

Figure 3. IL-1β (A) and IFN-γ (B) secretion by mononuclear cells from 11 normal controls, 7 HIDS patients and one MA patient. Cells were incubated for 18 hrs in the absence (left panel) or presence (right panel) of 5 µmol/l lovastatin and stimulated for 48 hrs with anti-CD2+CD28. Data are expressed as mean ± SD.
**Cytokine secretion is not augmented by addition of mevalonate**

To evaluate whether the augmented IL-1β and IFN-γ secretion was due to accumulated mevalonate in HIDS cells, the effects of exogenous mevalonate were studied in normal cells. In pilot experiments we had determined that 1 mM mevalonate was sufficient to overcome the antiproliferative effect of lovastatin without being toxic to the cells. In all subsequent experiments, the 1 mM concentration of mevalonate was used.

Mevalonate almost completely reversed the lovastatin effect on IL-1β production. In the absence of lovastatin, mevalonate induced no detectable effect on the secretion of IL-1β (figure 4A), IFN-γ (figure 4B) or IL-6. In fact, mevalonate decreased the inherently increased IL-1β secretion by HIDS and MA cells. This implies that an excess of mevalonic acid, is not responsible for increased cytokine secretion as observed in HIDS. This could be confirmed by the decrease in IFN-γ secretion by cells from controls and HIDS patients after incubation with lovastatin and mevalonate compared to incubation with lovastatin only. However, mevalonate does not affect the secretion of IFN-γ by MA PBMCs.

![Figure 4](image)

**Figure 4.** The effect of mevalonate on IL-1β (A) and IFN-γ (B) secretion by PBMCs from controls, HIDS and MA patients. Presented are the mean IL-1β and IFN-γ concentrations determined in independent incubations in the absence of presence of lovastatin using PBMCs obtained from 10 different controls, 4 HIDS patients and 1 MA patient. Data are expressed as mean ± SD.

**Isoprenoid compounds can reverse the effect of lovastatin downstream from mevalonic acid**

Mevalonic acid could abort the increase in cytokine secretion, mediated by impaired isoprenoid biosynthesis due to lovastatin or mevalonate kinase deficiency. To investigate whether this was an effect of mevalonic acid per se or one of its downstream metabolites, we studied the ability of FOH, GOH and GGOH to correct this increased secretion.

The lovastatin-induced increase in IL-1β secretion by PBMCs from control subjects could be reduced by FOH (p<0.01) either alone or in combination with GGOH (figure 5A). The 42% reduction brought about by GGOH by itself did not reach statistical significance. Also GOH tends to decrease IL-1β secretion in controls and seems to be most effective in decreasing IFN-γ secretion by control cells in the presence of lovastatin (figure 5D).
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Figure 5. Effects of isoprenoid pathway intermediates in the presence of lovastatin. IL-1β and IFN-γ secretion by PBMCs from controls (A, D), HIDS (B, E) and MA (C, F) patients incubated in the absence or presence of lovastatin, FOH, GOH and GGOH for 18 hours followed by stimulation with anti-CD2+ CD28.

Data are expressed as mean ± SD.
In the presence of lovastatin, IL-1β and IFN-γ secretion by PBMCs from HIDS patients was reduced by the addition of FOH and GGOH, but not by the addition of GOH (Figure 5B&E). This effect is comparable to that observed in normal controls. The single patient with MA displayed a similar pattern (Figure 5C&F). These results indicate that compounds downstream of mevalonate in the isoprenoid biosynthetic route can, at least in part, reverse the effect of lovastatin on IL-1β secretion. This implies that the lack of such compounds might be responsible for the increased cytokine secretion observed in the presence of lovastatin.

Figure 6. Effects of isoprenoid pathway intermediates in the absence of lovastatin. Cells were incubated in the presence of culture medium only, 10 µmol/l FOH, 10 µmol/l GOH and 10 µmol/l GGOH.
A. IL-1β secretion in HIDS patients (n=7, for GOH n=5)
B. IL-1β secretion in MA patient (n=1)
C. IFN-γ secretion in HIDS patients (n=6, for GOH n=4)
D. IFN-γ secretion in MA patient (n=1)
Data are expressed as mean ± SD.
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Isoprenoid compounds downstream from mevalonic acid reduce IL-1β and IFN-γ secretion in HIDS and MA

Apparently decreasing mevalonate availability by HMG-CoA inhibitors reduces isoprenoid output in HIDS and MA. This implies that, although affected patients are ill due to the reduced mevalonate kinase activity, there is an important residual MK activity and the enzyme does not become entirely and solely rate limiting.

The central question, therefore, was whether downstream isoprenoids could correct the inherently raised secretion of IL-1β and IFN-γ in HIDS and MA. Indeed, in the absence of lovastatin, i.e., with the endogenous MK deficiency being the only restriction on isoprenoid biosynthesis, downstream isoprenoids could reduce IL-1β secretion (Figure 6A&B). FOH significantly reduced IL1-β secretion by cells from HIDS patients by 62% (p < 0.02), addition of GGOH also reduces IL-1β and GOH did not affect the IL-1β secretion by HIDS and MA cells. Although less pronounced, IFN-γ secretion follows the same pattern as IL-1β secretion (Figure 6C&D).

Anti-CD2+CD28 induced T-lymphocyte proliferation is impaired by lovastatin

The rise in IL-1β secretion in culture supernatants could not be explained by higher cell numbers per culture well. Indeed, cell proliferation dropped in the presence of lovastatin (Figure 7). Mevalonic acid completely reversed this effect. GGOH partially corrected the effect of lovastatin. These data indicate that in this system lovastatin is effective and that its effect could be antagonized by downstream isoprenoids in the concentrations used.
Discussion

In recent years, the genes involved in 4 hereditary periodic fever syndromes have been identified (6;7;20-23). MEFV (the gene mutated in familial Mediterranean fever) and CIAS1 (the gene affected in familial cold-induced autoinflammatory syndrome, the Muckle-Wells Syndrome and chronic infantile neurologic, cutaneous, and articular syndromes) code for pyrin and cryopyrin, respectively. Both proteins are involved in IL-1β activation (17;24-29). In the TNF receptor-associated periodic syndrome (TRAPS), the link with inflammation is straightforward, since the affected gene encodes the 55-kd receptor for TNF-α. Blocking of IL-1β might prove to be beneficial in TRAPS (30), indicating that IL-1β might also play a role in TRAPS pathogenesis. In MA and HIDS, the picture is more complex. HIDS is a well-defined autoinflammatory disease (31). There are recurrent episodes of inflammation, reflected both in clinical signs and symptoms and in neutrophil leukocytosis and increased levels of acute-phase reactants (1). Between attacks, serum IgD and IgA levels are usually raised, and PBMCs from HIDS patients secrete increased amounts of proinflammatory cytokines, notably TNF-α and IL-1β. The gene affected in both conditions, MVK, encodes MK, an enzyme involved in isoprenoid biosynthesis. However, how MK deficiency causes inflammation is not currently known. The enzyme deficiency leads to an increase of its substrate, mevalonate, and may lead to a shortage of end products, the isoprenoids (Figure 1). We adapted a model developed by Montero et al (17) to test whether the increased cytokine secretion in HIDS could be explained by the elevated mevalonate levels and/or decreased isoprenoid production. In this model, isoprenoid output is reduced by lovastatin, which inhibits HMG-CoA reductase, the enzyme preceding MK in the isoprenoid biosynthetic pathway.

PBMCs, stimulated with M tuberculosis in the presence of lovastatin, reportedly secreted more IFN-gamma, IL-1β and IL-18 (17). In line with this and other studies (17;28;32), we found that lovastatin caused a 9-fold increase in IL-1β secretion in normal PBMCs using a combination of T cell-stimulating monoclonal antibodies against CD2 and CD28, although a similar effect on IFN-γ secretion did not reach significance.

Spontaneous IL-1β and IFN-γ secretion was elevated in PBMCs from patients with HIDS and the one patient with MA. The combination ofLovastatin and anti-CD2 + 28 induced a rise in IL-1β output in both patients and controls. To a lesser extent, lovastatin also induced a small increase in IFN-γ secretion. To test whether downstream isoprenoid metabolites could correct this hypersecretion of IL-1β and IFN-γ, we added either mevalonate, FOH, GOH or GGOH to the culture medium. Mevalonate and GOH correct all branches of isoprenoid synthesis; FOH corrects mainly protein farnesylation and, to a lesser extent, synthesis of other sterol and nonsterol isoprenoids; and GGOH predominantly corrects geranylgeranylation of proteins (figure 1).

Mevalonate reversed the lovastatin-induced increase in cytokine production. Downstream metabolites as FOH and GGOH largely compensate for the effect of lovastatin. This implies that some isoprenoid product(s) are necessary to prevent IL-1β and IFN-γ secretion in this system. Which isoprenoid end products are ultimately
involved and how these interact with inflammatory pathways is subject of current research. The finding that in HIDS cells that are largely MK deficient, inhibition of HMG-CoA reductase would be of any consequence and that mevalonate could correct the effect of lovastatin is intriguing. Apparently, the residual MK activity (2-8%) is sufficient for changes in the availability of mevalonate to be reflected in isoprenoid biosynthesis. Even in MA, the enzyme deficiency, though profound, is not absolute and can, to a certain degree, be overcome by raised mevalonate levels. Houten et al (33) showed that MA and HIDS cells compensate for the reduced MK activity by elevating their intracellular mevalonate levels through increasing HMG-CoA reductase activity. This increased HMG-CoA reductase activity was also downregulated when HIDS and MA cells were incubated with FOH, GGOH or mevalonate (33). Thus, in order to maintain the flux through the isoprenoid biosynthesis pathway it seems important to increase the intracellular mevalonic acid levels. The main question is, however, what this means for the situation in HIDS, i.e., in the absence of lovastatin. There, the endogenous MK deficiency is the only impairment to isoprenoid biosynthesis. Mevalonate decreased IL-1β and IFN-γ secreted by HIDS cells, but not the high IL-1β and IFN-γ levels secreted by MA cells. In MA cells extra mevalonate in the already massive pool of mevalonate, which is necessary to maintain the flux in the pathway, does not affect IL-β or IFN-γ secretion. Mevalonate, by itself, did not influence IL-β or IFN-γ secretion. These findings therefore indicate that mevalonate intoxication is not the cause of increased IL-1β and IFN-γ secretion by HIDS cells. Furthermore, we showed that, in the absence of lovastatin, FOH and to a lesser extent, GGOH could decrease IL-1β and IFN-γ production by HIDS cells, although those levels still remains elevated compared to control levels. This could be due to insufficient rescue of isoprenoid biosynthesis in this model. In that case, higher concentrations of isoprenoids than those used in the present study might be more effective. FOH and GGOH directly correct prenylation of proteins, which GOH might establish indirectly. Therefore GOH might be effective at higher concentrations than FOH or GGOH. There is presently no effective treatment for HIDS or MA. If excess mevalonic acid is the cause of symptoms, then treatment with statins could be beneficial. Recently, Simon et al. reported the outcome of simvastatin treatment of 6 patients with the HIDS phenotype, which led to shorter periods of fever in most patients (34). Experience with statins in MA has been disappointing, however, with severe inflammatory attacks apparently provoked by the drugs. This could be explained by failure of the compensatory mechanism of elevated intracellular mevalonate levels through increasing HMG-CoA reductase activity in MA cells (33). Also our own findings provide an explanation for this effect, since it is indeed the lack of downstream isoprenoids that contributes to increased IL-1β and IFN-γ secretion in HIDS.

Acknowledgements

We are grateful to the patients and their families for their participation in the study.
References


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