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Essential fatty acids as possible mediators of the actions of statins

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Summary Statins and polyunsaturated fatty acids have similar actions: both enhance endothelial nitric oxide synthesis, inhibit the production of pro-inflammatory cytokines, lower cholesterol levels, prevent atherosclerosis and are of benefit in coronary heart disease, stroke and osteoporosis. Statins enhance the conversion of linoleic acid and eicosapentaenoic acid to their long chain derivatives. Animals with essential fatty acid deficiency show an increase in HMG-CoA reductase activity, which reverts to normalcy following topical application of linoleic acid. Similarly to statins, polyunsaturated fatty acids also inhibit HMG-CoA reductase activity. In view of the similarity in their actions and as statins influence essential fatty acid metabolism, it is suggested that essential fatty acids and their metabolites may serve as second messengers of the actions of statins. © 2001 Harcourt Publishers Ltd

INTRODUCTION

HMG-CoA reductase inhibitors or statins inhibit the rate-limiting step in cholesterol biosynthesis and hence are used to lower cholesterol and prevent the development of atherosclerosis.[1] Recently, it has been recognized that statins are of benefit to patients with myocardial infarction even when they have no effect on cholesterol levels or formation of atherosclerosis,[4,5] prevent stroke,[2] and increase bone-mineral density in post-menopausal women.[3] These multiple actions of statins have been ascribed to their ability to enhance endothelial nitric oxide synthesis,[6] inhibit the production of pro-inflammatory cytokines, tumor necrosis factorα (TNFα)[7] and interleukin-6 (IL-6),[8] and C-reactive protein,[9] plasminogen activator inhibitor type-1 (PAI-1),[10] and monocyte chemotactic protein-1 (MCP-1).[11] Statins can increase the expression of bone morphogenetic protein 2 (BMP-2) and thus increase bone formation, even in postmenopausal women.[12] In addition, statins inhibit cellular proliferation, induce apoptosis of tumor cells in vitro, though they are of little use as anti-tumor agents in vivo in view of their selective hepatic uptake and low systemic availability.[13]

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EFAS HAVE ACTIONS SIMILAR TO STATINS

It is interesting to note that essential fatty acids (EFAs) and their metabolites such as gamma-linolenic acid (GLA, 18:3n-6), dihomo-GLA (20:3n-6), arachidonic acid (AA, 20:4n-6), eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) also have actions similar to statins. EFAs, linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA, 18:3n-3), are widely distributed in our diet.[14] Both LA and ALA are converted to their respective long-chain polyunsaturated fatty acids (PUFAs) by the enzymes: δ-6- and δ-5-desaturases. DGLA, AA and EPA form precursors to 1, 2 and 3 series of eicosanoids respectively. Similarly to statins, PUFAs can lower cholesterol, triglyceride and low density lipoprotein levels,[15] block HMG-CoA reductase activity[16,17] and enhance NO synthesis from the endothelial cells.[18,19] Marine PUFAs protect against ischemic heart disease,[20,21] inhibit platelet aggregation[22] and smooth muscle cell proliferation and thus, prevent atherosclerosis.[23] Similarly to statins, EFAs/PUFAs are useful in the prevention and treatment of osteoporosis,[24] and suppress the production of pro-inflammatory cytokines.[25,26] In view of the similarity in their actions, is it possible that statins and EFAs interact with each other?

EFAS AND STATINS

It has been shown that statins can enhance the conversion of LA and EPA to their long chain PUFA derivatives.[27] Animals with EFA deficiency showed an increase in HMG-CoA reductase activity, which reverted to normalcy following topical application of LA.[28] Further, PUFAs can inhibit HMG CoA reductase activity.[29–31] Hence, I suggest that statins bring about some, if not all, of their actions by interacting with EFAs and their metabolites and by augmenting EFA metabolism. It is possible that EFAs and their metabolites may serve as endogenous second messengers of statins.

In view of this, PUFAs and statins may form a potent combination in the treatment of a variety of disorders including, but not limited to, hyperlipidemias, atherosclerosis, stroke, ischaemic heart disease, osteoporosis, and possibly cancer. Such a combination may suppress inflammation and autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus in view of their action on pro-inflammatory cytokines. A combination of PUFAs and statins may particularly be useful in the treatment of cancer. This is so since mevalonate is not only the precursor of cholesterol but also of a variety of isoprenoid containing compounds, which are necessary for the posttranslational lipid modification (prenylation) and hence, the function of *ras* and other small GTPases.[13] Chapkin et al.[32] showed that n-3 PUFAs are capable of suppressing carcinogen induced *ras* activation in the colon prior to overt neoplasia. Furthermore, various PUFAs can selectively kill tumor cells by a free radical dependent process,[33–36] and by suppressing *Bcl-2* expression,[37] an anti-apoptotic gene.

Recently, it was suggested that statins can substantially lower the risk of developing dementia including Alzheimer's disease.[38] If this is true, even EFAs and their metabolites should also be useful in Alzheimer's disease. Yehuda and Carasso[39] showed that preparations with w3-to-w6 ratios ranging from 1:3.5 to 1:5 produced significant favourable effects on learning, pain thresholds and thermoregulation. On the basis of these results, it was opined that the beneficial effects of the PUFAs can be related to optimal incorporation of w3 fatty acids into the brain membranes. The presence of appropriate amounts of PUFAs in the neuronal membranes is important for their structural integrity, membrane fluidity, and membrane-related functions such as receptor, enzyme, and ion channel kinetics, as well as eicosanoid functions (reviewed in 39). It is also known that arachidonic acid and linolenic acid stimulate glucose uptake in cerebral cortical astrocytes.[40] Furthermore, hippocampal acetylcholine release during memory testing in rats can be potentiated by glucose.[41] This suggests that AA and ALA and, possibly, other PUFAs can improve memory by enhancing glucose uptake by neuronal cells, which in turn augments acetylcholine release, a molecule that is known to be involved in memory formation. This coupled with the observation that PUFAs are potent neuroprotectors,[42] DHA prevents neuronal apoptosis,[43] and low serum DHA is a significant risk factor for Alzheimer's disease,[44] indicates that provision of adequate amounts of various PUFAs (in the right proportion) can also prevent Alzheimer's disease and other dementias similarly to statins. Hence, it is likely that the beneficial effect of statins in the prevention of Alzheimer's disease and other dementias may also be due to their ability to enhance EFA metabolism. Furthermore, both statins and PUFAs have anti-inflammatory actions. Since inflammation is believed to play a major role in Alzheimer's disease, the anti-inflammatory actions of statins and PUFAs may contribute to their beneficial action(s) in Alzheimer's disease and other dementias. It is also known that small GTPases, which are prenylated products of the mevalonate pathway, may have a negative control on the expression of BMP-2 and other BMPs. Thus, inhibition of the mevalonate pathway by statins and PUFAs may prevent the function of small GTPases and enhance the expression of BMPs. It is now known that BMPs have multiple functions in the developing nervous system. Primary cells derived from the septal area of E14 mice when were treated with human recombinant BMP-2, BMP-4, BMP-6, BMP-7, BMP-9 and BMP-12 a several-fold increase in cellular acetylcholine levels was observed.[45] Further, BMP-9 directly induced the expression of the cholinergic gene locus encoding choline acetyltransferase and the vesicular acetylcholine transporter and up-regulated acetylcholine synthesis.[45] It is known that DHA increases cerebral acetylcholine levels and improves learning ability in rats.[46] It is possible that PUFAs are able to enhance brain acetylcholine levels by increasing the formation of BMPs as a result of their action on HMG-CoA reductase activity. Thus, it is suggested that both statins and PUFAs are able to improve memory and prevent Alzheimer's disease by augmenting the concentrations of BMPs in the brain.

In view of the similarity in their actions, it is suggested that combined administration of statins and PUFAs in the right proportion may prove to be highly beneficial in a variety of clinical conditions. Preliminary evidence for such potentiation of the action of statins by PUFAs in the treatment hyperlipidemias is already available.[47,48]

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