Cholesterol-Lowering Injectables: More Harm than Good?

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The nation's top nutrition advisory panel has now admitted, after 40 years of warnings about cholesterol consumption, that cholesterol is irrelevant to coronary heart disease risk,[1] but the pharmacological attack on cholesterol continues, only by a different pathway.[2]

Statins Block Mevalonate Pathway

Statin drugs lower cholesterol levels by blocking the mevalonate pathway, which is common to the synthesis not only of cholesterol but also ubiquinone (coenzyme Q10 or CoQ10), dolichols, selenoproteins, and several other biochemicals of extreme importance to cellular activity.

Statins are reductase inhibitors. The one reductase step in the 123-step pathway in cholesterol synthesis is quite easy to block. The potential for collateral damage is obvious. Apparently, the potential for immense profits distorted the ethical perspective of pharmaceutical manufacturers.

In their very first paper on the subject in 1973, C. Michael Brown and Joseph Goldstein[3] revealed that compactin (mevastatin), the first statin drug, which was not marketed, required the addition of non-cholesterol biochemicals like CoQ10, dolichols, and mevalonate to overcome the adverse effects of reductase inhibition that they had observed.

In 1978, Akira Endo, with Goldstein, Brown, and Faust, coined the phrase "the cells must adapt or die" to describe this effect of compactin because cells need both cholesterol and non-cholesterol mevalonate-based products to grow and replicate.[4] The cell's protective response of reductase enhancement indicated how critical this biochemical stepping stone is. The life of the cell is absolutely dependent upon it. Cholesterol, CoQ10, and dolichols are but a few of the many biochemicals critical to our various cellular processes.

Thus, as early as 1973 the warning signs were flashing about the critical importance of CoQ10 and dolichols. But when marketing of statins began in the 1980s, pharmaceutical corporation management ordered representatives to focus only on cholesterol. That was what statins blocked: only cholesterol. Not one word about CoQ10, dolichols, and all the other downstream effects. As far as doctors were concerned there were no collateral effects worth mentioning. Management blacklisted all the precautionary words and evidence about statins inhibiting the synthesis of CoQ10 and dolichols.

Just how important is CoQ10? It has three primary functions: cell wall integrity, anti-oxidation, and ATP formation.[5] Bursting with CoQ10 as children, we gradually lose our ability to synthesize it and increasingly depend upon diet. At about retirement age we have lost most of our ability to synthesize our own CoQ10, and the only significant dietary source is beef hearts. Statins eradicate what little CoQ10 synthesis remains, resulting in a variety of adverse effects that contribute to symptoms of fatigue and heart failure.

Dolichols are involved in an intricate process of cellular activity involving message transport, neuropeptide formation, and mitochondrial DNA error correction.[6] Physicians are baffled by the complaints of their statin-damaged patients because they are unaware of the chaos statins cause in cell function, resulting in a variety of adverse effects that contribute to symptoms of fatigue and heart failure. Dolichol inhibition contributes to a broad range of conditions such as myopathies, neuropathies, diabetes, and rhabdomyopathies. Pharmaceutical companies and the U.S. Food and Drug Administration also have a poor understanding. Marketing began based on very incomplete understanding.

Consider just the DNA error-correction function of dolichols. This involves a class of glycoproteins known as glycohydrolases.[7] A specific compound is required for every type of DNA error. Daily, our somatic and mitochondrial DNA files are searched and corrected. Tens of thousands of these errors occur daily in our process of normal metabolism and each one of these must be identified and corrected. The cell cannot, for example, tolerate the conversion of adenosine bases to uracil.

All this was learned from our first statin, compactin (ML-236B), which is produced by the fungus *Penicillium citrinum*. In 1976 Merck isolated our second statin, lovastatin (Mevacor, MK803), from the fungus *Aspergillus terreus,* and the various other statins in common use today were gradually developed.

Two studies illustrate the importance of the mevalonate pathway.

Do-sim Park and others at South Korea's University School of Medicine showed the effectiveness of mevalonate in preventing Zocor-associated cochlear neuronal damage in experimental animals.[8] It has been established that the commonly used statin drug, Zocor, induces extensive damage and death of cochlear neurons.[8] In this technically straightforward piece of research, cell cultures consisting of neurons from the organs of hearing of experimental animals were treated with Zocor in the absence or presence of mevalonate. All of the harmful effects were abolished by mevalonate treatment.

M. Azim Surani and others at the R.C. Institute of Animal Physiology, Cambridge, found that compactin, when administered to mouse embryos, consistently caused arrested development at about the 32-cell stage.[9] This effect was completely inhibited by mevalonate. Additionally, the authors noted excess inhibition of protein glycosylation during this process, pointing to impairment of dolichol synthesis and leading the authors to suspect that dolichols played a more significant role during embryonic development.

It appears to me that drug companies have hidden the truth in their marketing. It makes a big difference if representatives can say that their drugs simply block cholesterol rather than saying that statins block cholesterol, ubiquinone, dolichols, selenoproteins, nuclear factor-kappaB, rho, etc. But the deception may have begun in 1955, when we first labeled cholesterol our Public Health Enemy No. 1.

From my study of the adverse reactions of statins over the past 15 years, I have concluded that the primary adverse reactions from inhibiting cholesterol synthesis are cognitive in nature. Cholesterol is required for both the formation and function of our memory synapses. Frank Pfrieger identified it as the mystery substance for which he had been searching for two decades.[10] So vital is cholesterol for memory that our glial cells serve as a backup system for manufacturing additional cholesterol upon demand. He described cholesterol in our blood, bound as it is with a lipoprotein, as forming much too large a molecule to pass our blood-brain barrier. Hence it is not available to our brain. Our remaining glial cell resource for cholesterol synthesis is inhibited by statins with the lower-than-usual cholesterol resulting in unusual amnesias, memory lapses, confusion, disorientation, forgetfulness, and dementias, and possibly contributing to various degrees of depression and behavioral disorders.

To gain some insight into the magnitude of this problem, FDA's Medwatch report for the period 2006 to 2012 from all statins[11] includes 1,339 cases of cognitive deficit; 7,171 of confusion; 1,616 of irritability; 2,054 of disorientation; 1,577 of dementia; 4,810 of transient global amnesia; and 4,235 of memory deficit.

CoQ10 and dolichol deficiency cause most of the remaining side effects such as myopathies, peripheral neuropathies, ALS-like conditions, rhabdomyolysis, heart failure, and diabetes. Heart failure is clearly a consequence of insufficient CoQ10.[12] Siddals et al. concluded that diabetes was inevitable with statin use.[13] They report: "Statins disrupt cellular processes by the depletion of isoprenoids and dolichols. Insulin and insulin-like growth factor (IGF) signaling appear particularly prone to such disruption."

Other mechanisms of harm are many and varied. Muscle cell inflammatory breakdown with CPK elevations are commonly seen with severe myopathies, many of which lead to rhabdomyolysis.[14] Statin-associated autoantibodies to muscle are found in some five percent of myopathy cases.[15] Another common mechanism for cell damage of various types is mitochondrial DNA mutations caused by both CoQ10 and dolichol deficiency states.[15] The failure of effective anti-oxidation associated with CoQ10 deficiency leads to increased numbers of mitochondrial mutations, while the simultaneous lack of sufficient dolichol leads to failure of the glycohydrolase-mediated system to adequately correct them.

PCSK9 Inhibitors Reduce Just Cholesterol

The current interest of pharmaceutical companies in PCSK9 inhibitors suggests that they have, after 20 years, awakened to the reality of these adverse reactions resulting from mevalonate pathway blockade. But apparently they plan to keep flying their "Cholesterol: Public Health Enemy No. 1" banner. To do this they are developing injectable monoclonal antibodies against a newly discovered protein known as proprotein convertase subtilisin kexin 9, which dramatically reduces the amount of LDL cholesterol circulating in the bloodstream.[16] This avoids the mevalonate pathway, preserving our CoQ10, dolichols, selenoproteins, and all the rest. But cholesterol is not our enemy, but rather one of our most important biochemicals, especially for brain function.

There is no doubt that the present notoriety of cholesterol has all but obscured its physiological importance and necessity in our bodies. Cholesterol is not only the most common organic molecule in our brain; it is also distributed intimately throughout our entire body. It is an essential constituent of the membrane surrounding every cell. The presence of cholesterol in this fatty double layer of the cell wall adjusts the fluidity and rigidity of this membrane to the proper value for both cell stability and function. Additionally, cholesterol is the precursor for a whole class of hormones known as the steroid hormones that are absolutely critical for life as we know it. These hormones determine our sexuality, control the reproductive process, and regulate blood sugar levels, proper level of calcium, mineral metabolism, and production of bile acids.

Researchers everywhere are learning how extraordinarily complex and often surprising are the pathways that produce and metabolize cholesterol in our bodies. Admittedly, even after decades of study of this remarkable chemical, we still have much to learn. It was not until 2001 that Pfrieger and associates announced that cholesterol was the elusive synaptogenic factor responsible for the development of synapses, the highly specialized contact sites between adjacent neurons in the brain.[10] Neuronal transmission, the very essence of who we are, is absolutely dependent upon abundant cholesterol reserves.

The result of ignoring this information, besides profits, will likely be the creation of enormous numbers of cognitive disorders of all kinds. Neurocognitive problems, such as mental confusion or trouble paying attention, have already

been noted to be present in some of the study participants receiving PCSK9 inhibitors.[16] The PCSK9 monoclonal antibodies cut LDL cholesterol levels by an average of roughly 61% to 62% compared with placebo or standard therapy.[17] During the years 2004-2012 of our statin era, nearly 10,000 cases of transient global amnesia or severe memory loss have been reported to Medwatch.[11] What will happen if the median level of serum cholesterol approaches 50, the expected target level of cholesterol when this new class of drug is used with Lipitor and Zetia?

The FDA approved two PCKS9 inhibitors in the summer of 2015, alirocumbab and evolocumbab, solely on the basis of a surrogate endpoint, the lowering of LDL-cholesterol levels. There is as yet no evidence of efficacy for reducing cardiovascular events, nor is there information on long-term safety.[18] Premature and widespread overuse is predicted, based on four factors, write Rodriguez-Gutierrez et al.: (1) the treatment of statin intolerance by substituting PCKS9 inhibitors; (2) the return of LDL-cholesterol targets to guidelines and quality-of-care measures; (3) adding PCKS9 inhibitors in the case of "statin failure," the occurrence of a cardiovascular event; (4) the treatment of "nonadherence" to statins by replacing daily pill-taking with a subcutaneous injection every two to four weeks.[19]

The cost of the new agents is about 280 times greater than the out-of-pocket cost of statin drugs. The costs of dementia are devastating. Even the authors cautioning against premature use of this "exciting new class of cholesterol-lowering drugs"[19] do not mention the essential role of cholesterol in neurologic function.

Conclusion

Although some of the adverse effects of statin drugs are being more widely recognized, even if not always attributed to interrupting the mevalonate pathway, American medical authorities are still miscasting cholesterol as a villain rather than a compound essential for life. The drugs aimed at attacking cholesterol are in such widespread use that if the accepted theories about cholesterol are wrong, the drugs are a serious threat to the health of Americans, while providing limited or no benefit.

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