24(S),25-Epoxycholesterol—A Potential Friend

Ingemar Bjorkhem, Ulf Diczfalusy

According to current concepts, oxysterols are the physiological mediators of a number of cholesterol-induced metabolic effects (for a review, see Bjorkhem et al1). Most of the evidence for this is however still indirect, and there is a discrepancy between the great number of studies demonstrating potent effects of oxysterols under in vitro conditions and the few studies consistent with a regulatory effect in vivo. Oxysterol binding proteins and receptors are doubtless of regulatory importance in cholesterol turnover, but the physiological ligand(s) to the proteins have not yet been defined with certainty. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, the article by Wong et al2 gives strong support for the contention that the oxysterol 24(S),25-epoxycholesterol, an efficient activator of the nuclear receptor LXR in vitro, is an important mediator of statin-induced effects on cholesterol homeostasis in THP-1 macrophages.

The second important message is that the oxysterol 24(S),25-epoxycholesterol, produced through a shunt pathway in cholesterol synthesis, appears to be the mediator of the above statin-induced effects in the macrophages. That there is some production of 24(S),25-epoxycholesterol by macrophages in the basal state confirms a recent work by Rowe and collaborators.3 Both in the present work and in the work by Rowe et al, the formation of this oxysterol in cultured macrophages was found to increase when the cells were exposed to low concentrations of an inhibitor of 2,3-oxidosqualene:lanosterol cyclase. Partial inhibition of this enzyme was found to lead to increased channelling of the intermediates in cholesterol synthesis into the pathway leading to 24(S),25-epoxycholesterol. 24(S),25-Epoxycholesterol is known to be a potent activator of LXR in vitro, and accumulation of this oxysterol would thus be expected to cause increased expression of LXR target genes such as ABCA1 and ABCG1 and increased cholesterol efflux. In accordance with this, Rowe et al could show that a cyclase inhibitor within a certain concentration range has a clear inhibitory effect on foam cell formation.3 The possibility was discussed in that article that partial inhibition of the 2,3-oxidosqualene:lanosterol cyclase may represent a potential new strategy for the prevention of atherosclerosis.

It should be pointed out that the data given by Wong et al do not exclude other mechanisms than that involving 24(S),25-epoxycholesterol in the statin-induced regulation of the LXR target genes. This is not the first time that 24(S),25-epoxycholesterol has been ascribed an important function in regulation of cholesterol homeostasis. In a report from 1985, the levels of 24(S),25-epoxycholesterol in human liver were reported to be of the magnitude 2 μg/g liver, levels that would clearly be consistent with a regulatory function.4 In a study a decade later, Lund reported hepatic levels of this oxysterol to be about two orders of magnitude lower in mouse.5 In a more recent study,6 the levels of 24(S),25-epoxycholesterol in rat liver were also found to be very low, in the low ng per g liver range, in particular in the nuclear fraction. In contrast to the other oxysterols measured, however, the level of 24(S),25-epoxycholesterol increased with a factor of 2 after administration of mevalonate to the rats. It was suggested6 that the epoxide could be a key mediator of the effects of mevalonate, downregulating 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase posttranslationally by triggering

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degradation and transcriptionally by inhibiting activation of SREBP. In the present work, conclusive evidence is presented that 24(S),25-epoxycholesterol is formed in the macrophages studied, and that the levels are affected by the oxidocyclase inhibitor as well as by statins. With the experimental design used in the present work as well as in the previous study, recording radioactivity rather than mass, the quantitative aspects of the formation of the epoxide are difficult to evaluate. In particular it is difficult to compare the endogenous levels of the epoxide found in the macrophages with the levels used to affect the LXRα-mediated genes (10 μmol/L). It should be emphasized that quantitation of endogenous levels of 24(S),25-epoxycholesterol is not trivial, and it has been reported that this compound may not survive the temperature required for GC-MS analysis.

It is interesting to compare 24(S),25-epoxycholesterol with another oxysterol, 27-hydroxycholesterol, that has also been ascribed a role in regulation of cholesterol homeostasis in macrophages (for a review, see Bjorkhem et al.). This oxysterol is formed from cholesterol in the mitochondria by a cytochrome P-450 system present in most cells in the body. The two products, 27-hydroxycholesterol and cholestenoic acid, can flux out of the cell, enter the circulation, be taken up by the liver, and converted into bile acids. This mechanism represents an alternative to reverse cholesterol transport, and may be of particular importance in tissues with a low degree of vascularization, such as tendons and the eye lens. In addition to this, 27-hydroxycholesterol may have an antiatherogenic effect similar to that of 24(S),25-epoxycholesterol. Thus 27-hydroxycholesterol may also bind to LXR and may thus have some stimulatory effect on the cholesterol transporters ABCA1 and ABCG1.

Experimental evidence supporting that such a mechanism may be operating in cholesterol-loaded human macrophages has been presented by Fu et al. 27-Hydroxycholesterol is however a weaker ligand to LXR in vitro than is 24(S),25-epoxycholesterol, and the importance of such a mechanism is still uncertain. It should be pointed out that in the study by Fu et al no significant levels of 24(S),25-epoxycholesterol could be detected in the cholesterol-loaded macrophages, possibly because of the methodological problems pointed out by Wong et al. On the other hand, the THP-1 cells used by Wong et al appeared to have very low production of 27-hydroxycholesterol.

The levels of the two oxysterols, 24(S),25-epoxycholesterol and 27-hydroxycholesterol, are likely to reflect changes at two different levels. Increased cholesterol synthesis would be expected to increase the concentration of the epoxide, at least under conditions in which there is a partial inhibition of the cyclase. This would lead to activation of the antiatherogenic target genes of LXR. Increased accumulation of cholesterol would be expected to lead to decreased cholesterol synthesis with decreased formation of the epoxide. Such accumulation may however tend to increase formation of 27-hydroxycholesterol, leading to increased efflux of this cholesterol metabolite and possibly also to increased efflux of cholesterol by the LXR-mediated mechanism described by Fu et al. It was pointed out by Wong et al that human macrophages may produce different ligands for LXR depending on the supply of exogenous cholesterol versus the activity of the shunt pathway.

A general concern with LXR agonists as therapeutic agents is the potential to increase liver and plasma TG concentrations by activation of fatty acid synthase (for a review, see Lund et al and references therein). In the study by Rowe et al, however, increased synthesis of 24(S),25-epoxycholesterol had no significant effect on triglyceride accumulation in the macrophages studied.

We have previously written a review article entitled “Oxysterols. Friends, Foes or just Fellow Passengers.” It is evident from the present article by Wong et al and from the previous one by Rowe et al that 24(S),25-epoxycholesterol is a potential “friend,” and that attempts to increase levels of this compound in macrophages may represent a new strategy for prevention of atherosclerosis.

References

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