Niacin Mechanism of Action

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It is only recently that we have begun to understand many of the complexities of niacin's mechanism of action. Like most of lipid-modulating agents much of its action is mediated through nuclear transcription factors that regulate lipid homeostasis. Through some of its metabolites namely prostaglandins D2 and J2, niacin influences PPARs, especially the gamma isoforms. Since 1993 Cesare Sitori (of apoA-I Milano fame) has been calling niacin as well as fibrates, "fraudulent fatty acids" meaning they in essence trick PPARs into believing they are FA and PPAR agonism occurs (Eur J Clin Invest 1993;23:686-689). Only recently was the niacin receptor called HM74A, identified. By the way, no has discovered the natural ligand for HM74A. Lancet 2004; 363: 1892–94.

1) Classically it has been taught that niacin's main action is to inhibit triacylglycerol or triglyceride (TG) hydrolysis (lipolysis) in adipose tissue. By attaching to the niacin receptor (HM74A) in adipocytes, hormone sensitive lipase (now being called triglyceride lipase) is inhibited. This reduces lipolysis (hydrolysis of TG) resulting in less fatty acids (FA) being secreted into plasma. This reduction of FA denies the liver its main substrate of TG production. However although there may be a transient reduction in FA release from adipocytes it is now known there is within a few hours a sudden surge in FA release, which likely plays a role in the insulin resistance associated with niacin use.

2) Within hepatocytes niacin both induces beta-oxidation of fatty acids (burns fat) and inhibits FA synthesis (lipogenesis). This reduction of hepatic FA reduces the main substrate for TG synthesis. Arterioscler Thromb Vasc Biol. 1999;19:1051-1059.

3) Niacin inhibits the enzyme diacyl-glycerol acyl transferase 2 (DGAT2) which esterifies monoglycerol and diglycerol, crucial enzymatic steps for TG production. J. Lipid Res. 45 (2004) 1835–1845, Arterioscler Thromb Vasc Biol. 1999;19:1051-1059. Steps 2 and 3 are extremely similar to those of fibrates and likely are mediated by PPAR agonism. Some experts are now classifying niacin as a fibrate.

4) Apolipoprotein B 100 is the main surface apoprotein of the betalipoproteins and is synthesized in hepatocytes and is either lipidated with sterols, phospholipids and TG or immediately degraded through a ubiquination process. The niacin-induced reduction in TG synthesis clearly reduces lipid substrate available for lipidation of apoB leading to increased post-translational degradation of apoB and ultimately less VLDL particles are produced. Ultimately this leads to less IDL and LDL and a reduction in apolipoprotein B (a very significant CV risk factor). Arterioscler Thromb Vasc Biol. 1999;19:1051-1059

5) The reduced numbers of VLDLs, produced in patients using niacin are also less likely to be TG-rich: this reduces cholesteryl ester transfer protein (CETP) activity reducing less swapping (transfer) of TG for cholesteryl ester (CE) between VLDL and LDL and HDLs. This will increase LDL and HDL size. Larger LDLs make the surface apoB assume a conformation more amenable to recognition and endocytosis by LDL-receptors: hepatic internalization of apoB particles of which LDLs are by far the most numerous, is now termed indirect reverse cholesterol transport and of course leads to reductions in LDL-C, non-HDL-C, VLDL-C, LDL-P and apoB.

6) Reduction of large, TG-rich VLDLs improves many rheologic factors like blood viscosity, and likely lessens FA induced endothelial dysfunction.

7) Niacin's main metabolite is prostaglandin D2. In turn its metabolite is prostaglandin J2 which is a potent PPAR-gamma agonist. Thus Niacin will have PPAR gamma activity. This likely is associated with many of the FA actions described above as well some cardioprotection actions as follows:

In the liver PPAR gamma cross communicates with the Liver X receptor (LXR). LXRs main function is to prevent intracellular sterol toxicity. LXRs accomplish this through many functions including the increased esterification of free cholesterol to cholesteryl ester, via the enzyme

acylcholesterol acyl transferase (ACAT), and upregulation of several membrane sterol efflux transporters of the ATP Biding Cassette (ABC) Transporter family. Specifically, ABCA1 transporters efflux cholesterol from within cells into a cholesterol acceptor protein, namely apoA-I (the HDL precursor protein). Thus niacin induces the liver to rapidly lipidate the nascent HDL (prebeta) inducing its maturation into smaller and then large, more mature alpha- HDL particles (hepatic lipidation of HDLs will raise HDL-C, but is unlikely to be cardioprotective). Fortunately ABCA1 can also be expressed in arterial wall foam cells (sterol-laden macrophages). In the arterial wall, niacin through its metabolite induced PPAR gamma activity through cross-talk with the LXR would enhance macrophage RCT. Although macrophage RCT is cardioprotective, it does not affect the total HDL-C level. The PPAR gamma activity of niacin also causes an increase in expression of a scavenger receptor located in arterial wall macrophages called CD 36. This macrophage-receptor internalizes oxidized LDL particles leading to foam cell formation. However, the cholesterol within the macrophage can then be excreted into HDLs via the upregulated ABCA1. In review, niacin in effect makes the macrophages clear or internalize atherogenic LDLs, but immediately gets the cholesterol transferred to an HDL via induction of macrophage RCT. Biochemical Pharmacology 67 (2004) 411–419

8) Niacin inhibits hepatic lipase (HL). This is a major enzyme in the LDL and HDL remodeling process. By removing (hydrolyzing) TG and surface phospholipids HL remodels large TG-rich LDLs and HDLs into small particles. Because the niacin effect on HL reduces HDL lipolysis patients on niacin will typically have increases in the number of larger HDL particles (which carry more cholesterol). This is certainly another way Niacin raises HDL-C. Circulation. 1999;99:1959-1964.)

9) The liver has three receptors which play a role in the direct RCT pathway (HDLs returning cholesterol to the liver for delipidation or internalization). The hepatic scavenger receptor B1 (SR-B1) which attaches to and delipidates larger HDLs and then returns the empty smaller HDL to plasma is not affected by niacin. LDL receptors (LDLr) can internalize HDLs that are rich in apoE (usually large HDL species). Unlike statins or ezetimibe, niacin does not affect LDLr expression. There is also an HDL “holoparticle or catabolism” receptor (apoA-I beta chain synthase) which attaches to and internalizes (endocytoses) large HDL particles. This receptor is down-regulated by niacin enabling large HDLs to have a longer half life (clearly that would raise HDL-C and apoA-I and HDL-P). If the HDLs are functional (capable of performing macrophage RCT), it is likely beneficial for HDLs to have increased half-life’s as they would have more time to perform their multiple cardioprotective actions. Nature Vol 421 p 75 January 2003

With respect to macrophage RCT, it is preferable to have it performed by smaller, unlipidated apoA-I or prebeta HDLs. Unlike fibrates niacin does not increase production of apoA-I but rather by delaying the catabolism of the large HDL, increases the number of larger, mature alpha HDLs (explaining the rise in HDL-C so characteristic of niacin use). Arterial wall foam cells are complex cells capable of synthesizing multiple proteins involved with HDL remodeling, such as lipoprotein, endothelial and hepatic lipase and phospholipid transfer protein. As the niacin-induced large mature HDLs (each usually carrying 3-4 apoA-I molecules approach the foam cells they are subject to lipolysis and as they reduce in size, apoA-I disassociate. The now unlipidated apoA-I is in a perfect position to induce efficient macrophage RCT. Although macrophage RCT would not change HDL-C it would increase plaque delipidation.

10) Because niacin like fibrates is so good at reducing TG (as explained above) there will be less CETP activity. That would keep cholesterol within LDLs, leading to larger LDLs which are more amenable to hepatic LDLr internalization Of course niacin (and fibrates) to not reduce CETP activity anywhere near the level that torcetrapib (a powerful CETP inhibitor), a drug associated with CV as adversity) did. If one maximally upregulates LDLr (statins, ezetimibe, bile acid sequestrants), the shifting of LDL size would help maximize hepatic LDL particle endocytosis (indirect RCT) leading to synergistic reductions in VLDL-C, LDL-C, non-HDL-C, apoB and LDL-P.

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11) Niacin through mechanisms that are not well understood, but almost certainly related to its PPAR gamma agonism has multiple pleiotropic effects such as increasing adiponectin, reducing C-reactive protein (especially when combined with a statin) and lipoprotein associated phospholipase A2. It also seems to have antioxidant properties.

So if we had to sum up: here is niacin's lipid MOA and how it may or may not relate to cardioprotection.

1) Lower apoB, LDL-C and Non HDL-C through its TG lowering abilities

2) Improves HDL functionality by increasing macrophage RCT (which does not raise HDL-C)

3) Lipidates HDLs by upregulating hepatic ABCA1 and then keeps them mature (larger) by inhibiting HL: this raises HDL-C considerably but this increase does not likely explain niacin's cardioprotective actions. One might argue that it is better if the liver lipidates HDLs with cholesteryl ester rather than lapidating apoB particles (VLDLs).

4) Prevents hepatic delipidation of HDLs which increases the half life of circulating large HDL, increasing apoA-I and HDL-P: this of course also helps raise HDL-C and is likely cardioprotective if and only if those HDLs are functional and perform macrophage RCT (we have no way of assaying that). As speculated these larger HDLs may release unlipidated apoA-I upon exposure to foam cells.

5) Multiple pleiotropic effects

Since we cannot measure HDL functionality, I believe the most important test to follow that should ensure cardioprotection is apoB or LDL-P. Since the niacin induced rise in HDL-C is expected (I'd be alarmed if there was no HDL-C increase) but has no correlation with HDL functionality, I am not sure that following HDL-C on niacin tells you anything and thus following Non HDL-C or the TC/HDL-C ratio would not be as good as following apoB or LDL-P which is now recommended by ADA/ACC.

Although we still await serious, well empowered modern outcome data with niacin, we certainly have good data from very small trials that niacin added to a statin improves angiographic findings, lessens carotid intimal thickening and reduces clinical events and is well tolerated. We await confirmation of this in the much larger AIM HIGH trial which is underway. Clearly they are not seeing the 90% event reduction in AIM HIGH that occurred in HATS or the trial would have been stopped for ethical reasons.