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Nicotinic acid (niacin) receptor agonists: will they be useful therapeutic agents?

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Abstract

Nicotinic acid (niacin) favorably affects very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and lipoprotein (a) (LP[a]) and increases high-density lipoprotein (HDL). Emerging data indicates vascular anti-inflammatory properties to additionally account for niacin's proven effects in cardiovascular disease. Recent evidence indicates that niacin acts on GPR109A and GPR109B (HM74A and HM74, respectively), receptors expressed in adipocytes and immune cells. In adipocytes, GPR109A activation reduces triglyceride (TG) lipolysis, resulting in decreased free fatty acid (FFA) mobilization to the liver. In humans, this mechanism has yet to be confirmed because the plasma FFA decrease is transient and is followed by a rebound increase in FFA levels. New evidence indicates niacin directly inhibits diacylglycerol acyltransferase 2 (DGAT2) isolated from human hepatocytes, resulting in accelerated hepatic apolipoprotein (apo)B degradation and decreased apoB secretion, thus explaining reductions in VLDL and LDL. This raises important questions as to whether stimulation of GPR109A in adipocytes or inhibition of DGAT2 in liver by niacin best explain the reduction in VLDL and LDL in dyslipidemic patients. Kinetic and in vitro studies indicate that niacin retards the hepatic catabolism of apoA-I but not liver scavenger receptor B1-mediated cholesterol esters, suggesting that niacin inhibits hepatic holoparticle HDL removal. Indeed, recent preliminary evidence suggests that niacin decreases surface expression of hepatic beta-chain of adenosine triphosphate synthase, which has been implicated in apoA-I/HDL holoparticle catabolism. GPR109A-mediated production of prostaglandin D2 in macrophages and Langerhan cells causes skin capillary vasodilation and explains, in part, niacin's effect on flushing. Development of niacin receptor agonists would, theoretically, result in adipocyte TG accumulation (and clinical adiposity) and increased flushing. This raises questions about niacin receptor agonists as therapeutic agents. Several niacin receptor agonists have been developed and patented, but their clinical effects have not been described. Future research is needed to determine whether niacin receptor agonists will demonstrate all the beneficial properties of nicotinic acid on atherosclerosis and without significant adverse effects.

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