Niacin, an Old Drug, has New Effects on Central Nervous System Disease

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Abstract: Increased serum cholesterol and decreased high-density lipoprotein (HDL) cholesterol level in serum and cerebro-spinal fluid is a risk factor for the development of Alzheimer disease, and also a predictor of cardiovascular events and stroke in epidemiologic studies. Niacin (vitamin B_3 or nicotinic acid) is the most effective medication in current clinical use for increasing HDL cholesterol and it substantially lowers triglycerides and LDL cholesterol. This review provides an update on the role of the increasing HDL cholesterol agent, niacin, as a neuroprotective and neurorestorative agent which promotes angiogenesis and arteriogenesis after stroke and improves neurobehavioral recovery following central nervous system diseases such as stroke, Alzheimer's disease and multiple sclerosis. The mechanisms underlying the niacin induced neuroprotective and neurorestorative effects after stroke are discussed. The primary focus of this review is on stroke, with shorter discussion on Alzheimer disease and multiple sclerosis.

Keywords: Niacin, HDL, stroke, Alzheimer disease, multiple scleroses.

INTRODUCTION

The brain is the most cholesterol rich organ in the body. Cholesterol plays primary role in the regulation of synaptic function and neuronal cell plasticity, and is an essential modulator of the functional activity in physiological membranes [1]. Neuronal function in both the central and peripheral nervous systems depends on appropriate regulation of membrane structure and composition. Increased serum cholesterol and a low high-density lipoprotein (HDL) cholesterol level in serum and cerebro-spinal fluid is a risk factor for the development of Alzheimer disease [2].

Elevated serum low-density lipoprotein (LDL) cholesterol and low serum HDL cholesterol are also risk factors for atherosclerotic ischemic stroke [3]. Epidemiologic studies show that the HDL cholesterol level is a strong predictor of cardiovascular events and stroke [4]. Low levels of HDL cholesterol are associated with increased atherothrombotic events, including stroke. HDL cholesterol is a heterogeneous group of lipoproteins that diminishes LDL cholesterol in the bloodstream, decreases platelet aggregation, and inhibits endothelial cell apoptosis [5]. HDL cholesterol enhances endothelial cell migration and reendothelialization [6-9], promotes anti-inflammatory, anti-oxidative and anti-thrombotic effects [10, 11]. Increasing HDL cholesterol has beneficial effects in the prophylactic treatment of cardiovascular disease [10, 12]. In prospective epidemiologic studies, every 1-mg/dL increase in HDL cholesterol is associated with a 2% to 3% decrease in coronary artery disease risk, independent of LDL cholesterol and triglyceride levels [13].

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Emerging targets involved in raising HDL cholesterol level include lifestyle modifications, niacin (vitamin B_3 or nicotinic acid), fibrates, liver X receptor (LXR) and peroxisome proliferator-activated receptor (PPAR) agonists, cholesteryl ester transfer protein (CETP) inhibitors, HDL cholesterol mimetics, and Apolipoprotein A-I (Apo-AI) mimetic peptides [14-18]. This review provides an update of the increasing HDL cholesterol agent, niacin that facilitates neurobehavioral recovery and brain plasticity following central nervous system (CNS) diseases such as stroke, Alzheimer's disease and Multiple Sclerosis.

Niacin regulates multiple lipoproteins and has been used to treat atherosclerotic coronary heart disease and reduce the incidence myocardial infarction, stroke and atherosclerosis [11, 19-26]. Niacin is the most potent agent for raising HDL cholesterol in current clinical use. It also substantially reduces triglycerides and LDL cholesterol, and promotes a shift from small, dense LDL cholesterol to larger, more buoyant LDL particles. Raising HDL cholesterol with niacin therapy significantly improves endothelium-dependent vasodilatation in coronary heart disease patients with low initial HDL cholesterol [19]. Long-term follow-up from the Coronary Drug Project demonstrated that treatment with niacin reduced all-cause mortality by 11% ($P<0.05$) compared with placebo in 8341 men with coronary artery disease [27]. The Arterial Disease Multiple Intervention Trial Cholesterol combining niacin with a statin produces a greater reduction in cardiovascular risk in patients with diabetes and metabolic syndrome than statin monotherapy alone. Niaspan can be combined safely with statins and is also effective in patients with combined dyslipidemia and type 2 diabetes mellitus [29]. European Consensus Panel recommends the combination of niacin and a statin, together with lifestyle modification, as a useful strategy to lower coronary heart disease risk in patients with diabetes and metabolic syndrome [30]. Numerous studies have looked at the effects of niacin, alone and in combination with other

1877-3818/10

drugs, for the prevention of heart disease and fatal heart attacks [31]. This review focuses on the effects of niacin alone treatment on neurobehavioral recovery and brain plasticity following CNS diseases. Arterial disease multiple intervention trial (ADMIT) also shows that niacin may be administered successfully too many patients with diabetes and peripheral arterial disease who do not tolerate statins or fibrates [25]. Recent interest in niacin centers as an adjunct to statins and other therapies. Fixed-dose combinations of extended-release niacin with lovastatin are commercially available in the United States. Patients given niaspan (a slow release form of niacin) in combination with a low to moderate dose of lipitor or crestor achieved equivalent reduction in LDL cholesterol, 1.2 to 1.9-fold greater decreases in triglycerides and 2.5 to 3.5 fold greater increases in HDL, than patients who received high-dose Crestor or Zocor/Zetia [28].

MECHANISM OF NIACIN REGULATION OF LIPOPROTEIN:

Niacin increases HDL cholesterol (15-30% at clinically recommended doses), while it substantially lowers triglycerides and LDL cholesterol [25, 30, 32]. Niacin binds to adipose nicotinic acid receptors which down-regulates free fatty acid mobilization, as well as reduces hepatic very-low density lipoprotein (VLDL) output [33]. Niacin accelerates intracellular Apolipoprotein B degradation by inhibiting triacylglycerol synthesis in human hepatoblastoma cells [34]. Increasing HDL cholesterol levels by niacin through inhibition of the HDL Apolipoprotein A-I (Apo AI) catabolism pathway, thus prolonging HDL half-life [35]. Niacin also dose-dependently decreases the clearance of Apo AI from plasma and reduces the uptake of Apo AI by the kidneys (up to -90%) [36]. Niacin markedly increases HDL cholesterol in Apolipoprotein E*3Leiden cholesteryl ester transfer protein (CETP) mice by reducing CETP activity, as related to lower hepatic CETP expression and a reduced plasma VLDL pool [36]. Niacin also up-regulates LXR-alpha and peroxisome proliferator-activated receptor gamma mRNA expression and promotes the HDL-induced cholesterol efflux in adipocytes from hypercholesterolemic rabbits [37].

NIACIN TREATMENT OF STROKE INDUCES NEURORESTORATIVE EFFECTS:

Regulation of cerebral blood flow is critical for the maintenance of neural function [38]. Higher microvessel density in the ischemic border correlates with longer survival in stroke patients [39]. HDL cholesterol is implicated in the modulation of angiogenesis. Reconstituted HDL enhances ischemia-induced angiogenesis [40]. The higher levels of HDL cholesterol are associated with better functional performance in old people [41]. Low HDL predicts poorer cognitive function and greaterdisability after stroke [42]. Thus, agents that increase HDL cholesterol level may promote functional outcome after stroke. Niacin is the most potent HDL cholesterol-increasing drug used in the clinic. We have found that niaspan (a slow release form of niacin) treatment of experimental stroke in the rat starting 24h after stroke significantly increases HDL cholesterol, elevates local cerebral blood flow, and promotes angiogenesis and arteriogenesis and improves functional outcome [43, 44]. The increased arteriogenesis by niaspan treatment of stroke rats significantly correlated with functional outcome after stroke [44].

Mechanisms of Niacin treatment induced angiogenesis and arteriogenesis: HDL cholesterol promotes vascular wall function in coronary vessels and induces angiogenesis in human coronary artery endothelial and ovarian cells [45, 46]. HDL promotes endothelial cell migration and reendothelialization, which are mediated by activation of endothelial nitric oxide synthase (eNOS) and phosphoinositide-3-kinase (PI3K)/Akt kinase [8, 9]. Reconstituted HDL cholesterol stimulates differentiation of peripheral mononuclear cells to endothelial progenitor cells *via* the PI3K/Akt pathway and enhances ischemia-induced angiogenesis in a murine ischemic hindlimb model [40]. In addition, vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang1) with its Tie receptor (Tie2) are important angiogenic factors, which control angiogenesis to form large and small vessels in the mature vascular system [47]. Ang1/Tie2 cooperates with the VEGF system to establish dynamic blood vessel structures [48]. Hypercholesterolemic rats have decreased VEGF and Ang1 gene and protein expression and also a decreased ratio of phospho-endothelial nitric oxide synthase (p-eNOS) to eNOS compared to control rats [49]. Niaspan treatment of stroke increased the expression of VEGF and Ang1, and phosphorylation of Akt, eNOS and Tie2 in the ischemic brain [43]. Inhibition of PI3K or knockdown of Tie2 substantially and significantly decreased Niacin-induced capillary tube formation. The Ang1/Tie2, PI3K/Akt and eNOS pathway appear to contribute to Niacin-induced angiogenesis [43].

Endogenous eNOS-derived nitric oxide (NO) has a crucial role in the regulation of vascular tone, vascular remodeling, and angiogenesis [50, 51]. Enhanced eNOS phosphorylation induces a broad range of effects including the promotion of angiogenesis and mural cell recruitment to immature angiogenic sprouts [52, 53]. eNOS is not only associated with angiogenesis but is also related to arteriogenesis. $eNOS^{-/-}$ mice have defects in arteriogenesis and functional blood flow reserve after muscle stimulation and pericyte recruitment [52]. Arteriogenesis is regulated by NO, angiogenic factors and shear stress [54]. Hypercholesterolemia reduces collateral artery growth (arteriogenesis) more dominantly than hyperglycemia or hyperinsulinemia in mice [55]. HDL cholesterol causes potent stimulation of eNOS activity and also enhances endothelium- and NO-dependent relaxation in the aorta [56]. Elevated HDL cholesterol is associated with higher collateral grade in coronary artery disease [57]. HDL cholesterol binds to the HDL receptor scavenger receptor class B type I (SR-BI) and promotes eNOS expression and activity by maintaining the lipid environment in caveolae where eNOS is colocalized with partner signaling molecules [58]. Kuvin JT *et al.* found that Niacin promotes vasodilatation and improves endothelial function by enhancing the function of eNOS to increase plasma and tissue NO levels [6]. Niaspan increases HDL cholesterol level, angiogenesis and arteriogenesis after stroke, and promotes p-eNOS activity in the ischemic brain [43, 44]. In addition, Tumor necrosis factor-alpha (TNF-alpha) serves as a pivotal modulator of arteriogenesis, which is attenuated by treatment with TNF- α

inhibitors [59]. TNF-α converting enzyme (TACE) is the principal protease involved in the activation of pro-TNF-alpha [60] and regulates the function of several transmembrane proteins and cell adhesion molecular shedding [61]. Niaspan increases TACE expression which may play a role on regulation of arteriogenesis after stroke [44].

NIACIN IS CONVERTED TO NIACINAMIDE (ALSO KNOWN AS NICOTINAMIDE)

Niacin and nicotinamide are water-soluble B complex vitamins. Niacin is converted to nicotinamide, a constituent of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) *in vivo*, which are coenzymes involved in glycogenolysis, tissue respiration and lipid metabolism. Niacin is metabolized in the liver to nicotinamide. Nicotinamide is widely distributed in the body. Nicotinic acid and nicotinamide can penetrate the blood brain barrier [62]. Although the Niacin and nicotinamide are identical in their vitamin activity, nicotinamide does not have the same pharmacological effects as niacin, and does not reduce cholesterol, increase HDL cholesterol or cause flushing.

Nicotinamide, the amide form of Niacin, is the precursor for the coenzyme beta-nicotinamide adenine dinucleotide (NAD+) and is considered to be necessary for cellular function and metabolism. Nicotinamide also plays an important role on regulation of both neuronal and vascular cell populations in the brain injury. NAD (+) levels was significantly decreased in the ischemic brain in the early stages of developing cerebral infarction [63, 64]. Decreased NAD (+) levels preceded the appearance of neuronal apoptosis. Administration of nicotinamide 1-2 h after the onset of ischemia elevated brain NAD(+) levels, significantly attenuated necrotic and apoptotic brain injury after focal brain ischemia [65] and reduced ischemic infarct lesion [64, 66]. Delayed treatment with nicotinamide inhibited brain energy depletion, improved cerebral microperfusion [67] and protected hypertensive and hyperglycemic rats as well as wild type rats against a robust model of stroke [68, 69]. Nicotinamide also stimulates long-term survival and neuronal differentiation of chick embryo C cells [70]. Nicotinamide offers multiple protective mechanisms in stroke as a poly (ADP-ribose) polymerase (PARP) inhibitor and by partial restoration of mitochondrial function [71].

Niacin is already used clinically in large doses, and Niacin not only regulates cholesterol levels but is also converted to nicotinamide, which encourage the possible use of niacin and nicotinamide as a therapeutic neuroprotective and neurorestortive agent in the clinical treatment of ischemic stroke [68].

NIACIN EFFECTS ON MULTIPLE SCLEROSIS:

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system [72, 73]. During chronic CNS inflammation, NAD concentrations are altered by T helper-derived cytokines through the coordinated induction of both indoleamine 2,3-dioxygenase (IDO) and the ADP cyclase CD38 in pathogenic microglia and lymphocytes [74]. Brain macrophage/microglial respiratory chain enzyme activity in experimental autoimmune encephalomyelitis of the Lewis rat is significantly decreased [75]. 6-Aminonicotinamide, an antagonist of niacin and a potent CNS glio-toxin, selectively caused degeneration of glial cells in the CNS of rodents [76].

Niacin plays an important role in myelination associated with the synthesis of cerebrosides which contain high levels of long chain fatty acid [77, 78]. Niacin activates the G-protein coupled receptor GPR109a to produce the IDO-inducing tolerogenic prostaglandins PGE (2) and PGD (2). PGD (2) is converted to the anti-inflammatory prostaglandin. These prostaglandins exert potent anti-inflammatory activities [79]. Niaspan treatment experimental autoimmune encephalomyelitis (EAE) mice significantly reduce inflammatory infiltrates and demyelination areas, and stimulate oligodendrogenesis and axonal regeneration [80]. Neurological functional recovery was significantly increased when treatment of EAE mice with niaspan starting on the immunization or clinical onset day [80]. In addition, nicotinamide, an NAD biosynthesis precursor, profoundly prevents the degeneration of demyelinated axons and improves the behavioral deficits in EAE models [81]. Nicotinamide profoundly ameliorates and prevents autoimmune-mediated demyelination in EAE *via* maintaining levels of NAD, without activating PPAR nor any G-protein-coupled receptor [82]. Therefore, niacin and nicotinamide may be a target for MS treatment.

NIACIN EFFECT ON ALZHEIMER DISEASE

Total cholesterol and LDL are significantly related to pathologically defined Alzheimer Disease [83, 84]. High serum cholesterol levels induce the elevation of brain Apolipoprotein E, which plays a role in aggravating the Abeta accumulation [85]. Merched *et al*. have shown that ApoAI levels were significantly lower in Alzheimer Disease patients and were highly correlated with mini-mental state scores of Alzheimer Disease patients [86]. In addition, cellular cholesterol modulates axon and dendrite outgrowths and neuronal polarization [87], and cellular cholesterol homeostasis are causally involved in different steps leading to pathological events in the brain of Alzheimer Disease patients. Cellular cholesterol levels modulate Abeta generation, whereas Abeta alters cholesterol dynamics in neurons, leading to tauopathy [88]. Abeta is formed from the amyloid precursor protein (APP) in cholesterol-enriched membrane rafts, and cellular cholesterol depletion decreases Abeta formation [89]. Increasing membrane cholesterol in immature neurons might render mature hippocampal neurons sensitivity to β-amyloid (Aβ)-induced calpain activation and tau toxicity [90]. In addition, the risk of amyloid deposition associated with high cholesterol may be through induction of the Liver X receptors (LXR) system [91]. T0901317, a LXR agonist, decreases amyloidogenic processing of APP *in vitro* and *in vivo* [92]. LXR agonists facilitate the clearance of Abeta42 and represent a novel therapeutic approach to Alzheimer's disease [93]. Niacin up-regulates LXR-alpha and peroxisome proliferator-activated receptor gamma (PPARgamma) mRNA expression and promotes the HDL-induced cholesterol efflux [37]. Therefore, niacin decreases serum and cellular cholesterol levels, which may play a role on protection of Alzheimer's disease. Dietary niacin regulates learning performance, and prevents or reverses

cognitive decline [94], protects against Alzheimer Disease and age related cognitive decline [95]. Dietary niacin has been implicated as a protective factor against cognitive decline and Alzheimer's disease [96].

NAD (+) plays an essential role in important biological reactions. Chronic oxidative stress is associated with NAD (+) depletion and a subsequent decrease in metabolic regulation and cell viability [97]. The pyridine nucleotide NAD+ is derived from dietary Niacin and serves as the substrate for the synthesis of cyclic ADP-ribose (cADPR), an intracellular Ca signaling molecule that plays an important role in synaptic plasticity in the hippocampus, a region of the brain involved in spatial learning. Dementia can be caused by severe niacin insufficiency. Nicotinamide selectively reduces a specific phospho-species of tau (Thr231) that is associated with microtubule depolymerization. Nicotinamide also increased acetylated alpha-tubulin, which are linked to increased microtubule stability and restores cognition in Alzheimer's disease in transgenic mice [98]. Hence, therapies targeted toward maintaining intracellular NAD (+) pools and cellular cholesterol levels may prove efficacious in the protection of age-dependent cellular damage, and neurodegeneration in chronic central nervous system inflammatory diseases such as Alzheimer's disease [97].

SUMMARY

Niacin has multiple effects, among which are increasing HDL cholesterol, inhibiting inflammation, promoting vascular remodeling, which in concert support consideration of using niacin (niaspan) as a therapy for neurological injury and diseases, such as stroke, multiple sclerosis, vascular dementia and Alzheimer's disease.

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