Nicotinic acid: a lipid-lowering agent with unrealized potential
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Nicotinic acid is a well-known treatment for dyslipidemia in adults. This review article explored not only the role of nicotinic acid in dyslipidemia but also its role in hypertension and as a cardioprotective agent. Adverse effects in association with nicotinic acid use are described with a focus on flushing, the major reason for the discontinuation of nicotinic acid therapy. The role of nicotinic acid receptor in mediating its metabolic and vascular effects is also reviewed.

Keywords: cardiovascular protection, dyslipidemia, flushing, nicotinic acid

Introduction
Nicotinic acid, or niacin, an essential nutrient of the vitamin B complex group, is a well-known treatment for dyslipidemia in adults. It is highly effective in increasing the level of high-density lipoprotein (HDL) cholesterol and has been beneficial in reducing cardiovascular events in patients with dyslipidemia [1]. However, its clinical use has been limited because of the adverse event of flushing. Over the last few years, efforts have been made to understand the mechanisms underlying the metabolic and vascular effects of nicotinic acid. Research is aimed at inhibiting the niacin-induced flush, which has been proven to be critically important in improving tolerability and compliance [2].

Mechanism of action in dyslipidemia
It is well known that nicotinic acid improves the lipoprotein profile by decreasing the synthesis of low-density lipoprotein cholesterol through a reduction in the hepatic synthesis of very low-density lipoprotein cholesterol, an increase in the synthesis of HDL cholesterol, the inhibition of lipolysis in adipose tissue, and by an increase in lipase activity [3].

Recent research has presented other modes of action for niacin, which can be summarized as follows: (a) the inhibition of hepatic diacylglycerol acyltransferase 2, resulting in the inhibition of triglyceride (TG) synthesis and decreased apolipoprotein B-containing lipoproteins; (b) a decrease in the surface expression of hepatic ATP synthase β-chain, leading to decreased holoparticle HDL catabolism and increased HDL levels; and (c) an increase in the redox potential in arterial endothelial cells, resulting in the inhibition of redox-sensitive genes [4]. Another mechanism of action that was reported by Kostner and Gupta [5] is the modulation of liver TG synthesis, which leads to increased intracellular apolipoprotein B degradation and increased TG lipolysis in adipose tissue.

A classification of the effects of nicotinic acid on the basis of the onset and duration of action was presented by Bodor and Offermans [6]. They reported that the most rapid effect is a decrease in the plasma levels of free fatty acid, which can be observed within minutes of administration of the drug. After a few hours, the plasma very low-density lipoprotein and TG levels are reduced, whereas low-density lipoprotein and HDL cholesterol levels only change after several days of treatment. A recent study related the beneficial long-term effects of nicotinic acid to macrophages through an increased expression of peroxisome proliferator-activated receptor-G and enhanced peroxisome proliferator-activated receptor-G transcriptional activity in macrophages. However, further verifications are still required for the latter effect [7].

Role in hypertension
The role of niacin as an antihypertensive agent is still debatable. Previous research on the chronic blood pressure (BP) effects of niacin and niacin-containing regimens showed either no clear significant effects of niacin or a slightly lower mean BP among some niacin treatment groups compared with the placebo. Other clinical trials involving coadministration of the prostaglandin D2 (PGD2) receptor antagonist, liaripiprant, suggest that niacin may have dose-dependent chronic BP-lowering effects, which are unlikely to be because of the DP1 receptor activation leading to vasodilatation [8]. Other clinical trials that studied acute niacin administration showed significant BP-lowering effects in patients with hypertension but not in normotensive individuals [8]. The mechanism for the lowering of BP following the acute administration of immediate-release niacin is acute vasodilation, but the mechanism responsible for
the chronic lowering of BP by niacin is still unclear. One possibility is that niacin may lower the BP because of favorable lipid-altering effects that might improve endothelial function [9].

Recent research concluded that the administration of extended-release nicotinic acid alone or in combination with laropiprant was associated with significant and sustained reductions in systolic blood pressure and diastolic blood pressure in hyperlipidemic, hypertensive, and normotensive individuals compared with the placebo. The researchers reported that the BP-lowering effect of niacin is not mediated by PGD2 as it was not affected by the addition of laropiprant, which causes a reduction in PGD2-mediated flushing but does not affect the BP-lowering effect of extended-release niacin [9].

Niacin: a cardiovascular protective agent

It is well known that nicotinic acid has favorable lipid effects, as shown by the Coronary Drug Project, which reported a 10% reduction in total cholesterol and a 26% reduction in TG levels at the 6-year follow-up, as well as reduced cardiovascular disease risk and overall mortality rates [10,11].

With increased awareness of the role that low HDL cholesterol levels play as a risk factor for cardiovascular diseases, the strong HDL cholesterol-elevating effect of nicotinic acid has resulted in increased interest in the pharmacological properties of this drug and its role as a cardiovascular protective agent. Clinical trials concluded that as monotherapy or in combination with other lipid-altering agents, niacin is associated with reduced cardiovascular events and progression of atherosclerosis in patients with cardiovascular disease and dyslipidemia [12,13].

In 2010, a meta-analysis on the effect of nicotinic acid alone or in combination on cardiovascular events concluded that niacin alone or in combination exerts positive effects on all cardiovascular events and on the evolution of atherosclerosis. The same meta-analysis also reported that nicotinic acid decreased both coronary events and stroke, with similar risk reductions [14].

In the long-term follow-up of the Coronary Drug Project, it was proven that the administration of nicotinic acid alone or in combination with statins or bile acid resins, or both, to patients with cardiovascular disease or who were at an increased risk of cardiovascular disease significantly reduced the frequency of cardiovascular events, the progression to atherosclerosis, and overall mortality rates [10,11]. Further research confirmed these findings [15–17].

What makes nicotinic acid even more effective as a cardiovascular protective agent is its effect in reducing the plasma concentration of lipoprotein Lp (a), which has been suggested to play a role as an independent risk factor for coronary heart disease [18]. It is also possible that some of nicotinic acid’s cardiovascular outcome benefits may be related to an improvement in high BP, which is a major cardiovascular disease risk factor [8].

Formulations

Nicotinic acid has three main formulations: immediate release, extended release, and slow release [2].

The nicotinic acid receptor

With the recent discovery of a nicotinic acid receptor [19–21] following the demonstration of specific binding sites for nicotinic acid on the plasma membranes of adipocytes and spleen cells [22], it has become possible to better understand the mechanisms underlying the metabolic and vascular effects of nicotinic acid. The receptor GPR109A, also referred to as HM74A, is also expressed in various immune cells, including monocytes, macrophages, dendritic cells, and neutrophils [21–24]. The GPR109A receptor is coupled to Gi-type G proteins, and its activation by nicotinic acid results in a Gi-mediated inhibition of adenyl cyclase, resulting in a decrease in intracellular cyclic AMP levels, the principal mediator of adipocyte lipolysis. On the basis of these recent insights into the action of nicotinic acid, novel strategies are currently being investigated to maximize the pharmacological potential of this drug. Targeting the nicotinic acid receptor by new drugs and introducing new flush-reducing comedications of nicotinic acid could provide future therapeutic options for the treatment of dyslipidemia [22].

Side effects of nicotinic acid

Several adverse effects were described in association with the use of nicotinic acid. However, it has been agreed that flushing is the major reason for the discontinuation of nicotinic acid therapy, estimated to be at rates as high as 25–40% [2,25–27]. Kostner and Gupta [5] confirmed that the major adverse event of nicotinic acid is flushing, adding that this can not only be a cause of discontinuation but also of not reaching the target doses of this drug.

Niacin-induced flushing is primarily mediated by PGD2. The chief sources of increased PGD2 in patients with niacin-induced flushing are most probably niacin-responsive immune cells in the skin [28,29]. PGD2 binds to two G-protein-coupled receptors:
DP1 and DP2. Activation of DP1 by PGD2 induces vasodilation [30] and patients who failed to flush with nicotinic acid showed significantly reduced levels of arachidonic and docosahexaenoic acids [31]. Recent research found that nicotinic acid-induced flushing results from the GPR109A-mediated production of prostaglandin D2 and E2 in Langerhans cells, which act on DP1 and EP2/4 receptors in dermal capillaries, causing their vasodilatation [32–34]. Papaliodis et al. [35] suggested that both PGD2 and serotonin may be involved in niacin-induced flushing.

Having discussed the mechanisms involved in niacin-induced flushing, it is worth mentioning that niacin's PGD2-mediated flushing pathway is independent of the lipid-modifying pathway [29]. This means that the development of an agent that inhibits PGD2-mediated flushing without interfering with niacin's beneficial lipid-modifying effects is possible [36].

Other side effects of niacin include hepatic toxicity, which is largely confined to the use of slow-release formulations administered as unregulated nutritional supplements, insulin resistance, although the glycemic response in individuals with and without diabetes is usually minor, indicating that niacin can be used safely in patients with diabetes, blurred vision, nausea and vomiting, and the exacerbation of peptic ulcers.

A few studies have reported myopathy associated with niacin–statin combination therapy; however, there is no sufficient clinical evidence to support the myopathic effect of niacin either alone or in combination with statins. The reported number of laboratory abnormalities is small (≤10%) and may include a decrease in platelet count and serum phosphorus [37].

**Increasing tolerability: the role of laropiprant**

Despite its proven potency as an effective agent in the management of dyslipidemia, niacin-induced flushing limits its wider use. Flushing often persists with chronic treatment, and tolerance may be lost upon even a brief discontinuation of niacin [38–40]. Previous approaches toward reducing niacin-induced flushing showed limited success. The strategies used were either behavioral or pharmaceutical. Examples of behavioral strategies include the timing of medication (with meals, bedtime) or avoiding alcohol or spicy foods [41]. One pharmaceutical approach included the use of different formulations to reduce the rate of absorption [38,39,42,43], but this strategy was of limited value because the efficacy may be lost and hepatotoxicity may be increased. Another approach was the coadministration of aspirin and certain nonsteroidal anti-inflammatory drugs [38–40,44]. However, daily aspirin doses of 325 mg have to be administered 30 min before the niacin dose, which is considered a limitation to long-term use [44,45]. Besides, nonsteroidal anti-inflammatory drugs have modest effects in reducing niacin-induced flushing [45].

Recent research has attempted to provide an understanding of cutaneous flushing on the basis of the best available evidence, aiming to enhance patient education efforts and to improve compliance.

Research that explored this area and suggested possible solutions for overcoming niacin-induced flushing, aimed at improving tolerability and compliance, can be classified into three categories. The first category includes studies that focused on formulations that led to the reformulated preparation of extended-release niacin, which is more effective in reducing flushing compared with older formulations [32].

The second category of studies was concerned with further exploration of the role of aspirin pretreatment in the attenuation of flushing resulting from extended-release nicotinic acid use. Recent studies confirmed that aspirin reduced the number of flushing episodes and decreased the discontinuation rates compared with a placebo [26,32].

The third category studied the suppression of niacin-induced vasodilation with an antagonist to the PGD2 receptor subtype 1, introducing laropiprant, the new antiflushing agent [8,9,27,32,36,46,47]. Researchers in the latter category concluded that treatment with laropiprant plus extended-release niacin was well tolerated and led to a significant reduction in extended-release niacin-induced flushing at the initiation of therapy and in the long-term maintenance of therapy, without affecting the beneficial effects of nicotinic acid on lipids [27,48]. Moreover, the incidence of discontinuation was lower in patients who used laropiprant plus extended-release niacin compared with extended-release niacin alone [27,48]. Laropiprant also has good tolerability when administered alone or when coadministered with extended-release niacin. The incidence of side effects, either clinical (myopathy, hepatic toxicity) or in the laboratory (alanine aminotransferase, aspartate aminotransferase, creatine kinase elevations, alterations in glycemic regulations), was not increased with the coadministration of laropiprant compared with extended-release niacin used alone [26,48,49].

The improvement in the tolerability of extended-release niacin/laropiprant by directly targeting the flushing
pathway allows niacin dosing to be directly initiated at 1 g and rapidly advanced to a 2 g target dose, a therapy proven to reduce cardiovascular risk [47,48]. Some clinical trials aimed to study the effect of the addition of aspirin to the niacin/laropiprant therapy. However, the results have not shown a further reduction in the residual flushing symptoms associated with extended-release niacin 2 g/laropiprant 40 mg alone [50].

Conclusion and recommendation
Nicotinic acid is a potent lipid-lowering agent that also has beneficial cardiovascular effects. It is possible that it has antihypertensive potential, a property that needs further assessment. Despite this, the above-mentioned benefits of its use have been limited by suboptimal tolerability, mainly because of flushing. Multiple strategies have been used to overcome this problem. The most recent and most effective is the coadministration of laropiprant with niacin. The reductions in flushing observed with this cotherapy should facilitate the more widespread use of niacin at a more effective dose that will help to reduce the risk of cardiovascular disease in patients with dyslipidemia. Further studies are required in order to explore the role of the nicotinic acid receptor in mediating and ameliorating the therapeutic actions and side effects of nicotinic acid.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

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