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Review

Effects of formulation design on niacin therapeutics: mechanism of action, metabolism, and drug delivery

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ABSTRACT

Niacin is a highly effective, lipid regulating drug associated with a number of metabolically induced side effects such as prostaglandin (PG) mediated flushing and hepatic toxicity. In an attempt to reduce the development of these adverse effects, scientists have investigated differing methods of niacin delivery designed to control drug release and alter metabolism. However, despite successful formulation of various orally based capsule and tablet delivery systems, patient adherence to niacin therapy is still compromised by adverse events such as PG-induced flushing. While the primary advantage of orally dosed formulations is ease of use, alternative delivery options such as transdermal delivery or polymeric micro/nanoparticle encapsulation for oral administration have shown promise in niacin reformulation. However, the effectiveness of these alternative delivery options in reducing inimical effects of niacin and maintaining drug efficacy is still largely unknown and requires more in-depth investigation. In this paper, we present an overview of niacin applications, its metabolic pathways, and current drug delivery formulations. Focus is placed on oral immediate, sustained, and extended release niacin delivery as well as combined statin and/or prostaglandin antagonist niacin formulation. We also examine and discuss current findings involving transdermal niacin formulations and polymeric micro/nanoparticle encapsulated niacin delivery.

Contents

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1. Introduction

Nicotinic acid (niacin) is a water soluble, lipid regulating compound used in medical practice to lower circulating blood triglycerides (TGs) and reduce low density lipoproteins (LDL) (Sanyal et al., 2007). Niacin exerts its effects through alterations in key enzymatic pathways that regulate TG and LDL synthesis; while elevating the levels of high-density lipoproteins (HDL) (Kamanna and Kashyap, 2008). It has been postulated that niacin side effects are induced through interactions with the G protein-coupled receptor (GPR) 109A (Kamanna et al., 2009). When activated, this niacin receptor functions by increasing release of arachidonic acid and prostaglandin synthesis, thereby activating vasodilatory prostaglandin receptors resulting in the niacin-associated flushing. The beneficial effect of niacin on TG and LDL regulation is often offset by the vascularization effect within dermal skin cells (Pike, 2005). As such, the control and avoidance of niacin-induced vascularization and flushing is paramount to regulating patient compliance during treatment as the utility of niacin therapy is severely limited by patient non-adherence brought forth by flushing effects (Rhodes et al., 2013). To offset side effect development, several forms of oral drug delivery have been used, with varying results, to control niacin release (Moon and Kashyap, 2002; Rhodes et al., 2013). The first available form of niacin was termed immediate-release (IR) as the drug was a crystalline powder which dissolved upon administration (Pieper, 2003). Following IR, two forms of controlled release, sustained-release (SR) and extended-release (ER), were developed. Of note, the definition of the terms “ER formulations” and “SR formulations” in this review article are those commonly found in the literature on niacin. They are different from those usually applied in the field of controlled drug delivery/pharmaceutical technology. In this article, ER formulations are defined as systems exhibiting release rates, which are intermediate between those of IR and SR niacin formulations. SR formulations have been used to reduce flushing; however, these formulations present with hepatotoxicity as will be discussed (Piepho, 2000). The combination drug Advicor (ER niacin and lovastatin) has been used with promising results (Bays, 2004; Moon and Kashyap, 2002); however, even with ER formulation, oral delivery of niacin has been problematic in regard to flushing onset and patient adherence (Moon and Kashyap, 2002; Rhodes et al., 2013). This review will focus on the mechanistic functions of niacin in regard to modulation of dyslipidemia and atherosclerosis. Focus will also be given to methods used in drug reformulation to offset niacin-induced flushing and novel attempts used for improving niacin side effects as it relates to alternative drug delivery.

2. Clinical significance

Niacin is an important therapeutic option for the treatment of atherosclerosis and dyslipidemia (Linke et al., 2009; Pieper, 2003; Villines et al., 2012). To date, it is the only available agent that has been shown to favorably impact all lipid profile parameters (Clark and Holt, 1997; Knopp, 1998; Pieper, 2003). Niacin has been found to effectively lower LDL cholesterol, reduce TGs, and raise beneficial HDL cholesterol (Ito, 2002; Linke et al., 2009). The drug can also reduce lipoprotein a (Lp(a)) levels, an independent risk factor for the development of atherosclerosis (Berglund and Ramakrishnan, 2004; Carlson et al., 1989; Chennamsetty et al., 2012; Noma et al., 1990). Aside from the previously mentioned effects on serum lipid levels, niacin affects overall lipid particle size by reducing LDL particle size and increasing cardio-protective HDL levels (Ding et al., 2014; Sakai et al., 2001).

The overall effects of niacin on lipid parameters have clinical importance, as niacin has been found to significantly reduce cardiovascular events and slow progression of cardiovascular disease (The Coronary Drug Project Research Group, 1975; Barter, 2011; Brown, 2005). In 1955, it was discovered that niacin given in gram doses could lower plasma levels of cholesterol (Ganji et al., 2003). Furthermore, the discovery that niacin can up-regulate HDL levels to a greater degree than other cholesterol lowering agents has led to its wide spread use for treatment of dyslipidemia (Ganji et al., 2003; Villines et al., 2012). Due to its effectiveness, niacin has been used in numerous clinical studies to document its impact on a variety of coronary diseases (The Coronary Drug Project Research Group, 1975; Canner et al., 1986; Ruparelia et al., 2011). The largest study conducted to date on niacin and coronary artery disease, entitled “The Coronary Drug Project” was performed from 1966 to 1975 (Canner et al., 1986). In the study, a total of 1119 men between the ages of 30 and 64 all with past myocardial infarction were treated with 3 g of niacin daily. Niacin supplementation was found to have effectively lowered total cholesterol by 10% and TGs by 26% following 1 year of treatment. It was also noted that recurrent myocardial infarction was decreased by 27% compared to the placebo control group (Ruparelia et al., 2011).

3. Mechanism of action

Niacin has been found to operate through a variety of different pathways. In this section, we will discuss niacin’s method of action occurring through specific enzyme inhibition, and interactions with GPR109A.

3.1. Lipid modulation

Niacin’s anti-atherogenic mechanism of action is thought to involve multiple pathways of TG synthesis (Kamanna et al., 2009). Niacin functions to inhibit TG lipolysis, reducing free fatty acid (FFA) formation and subsequent release into systemic circulation. In turn, reduction of FFA leads to decreased levels of liver substrate to initiate hepatic TG synthesis. Niacin has also been shown to directly inhibit hepatic TG synthesis (Ganji et al., 2004; Guyton, 2004). Diacylglycerol acyltransferase-2 (DGAT2) is a key enzyme involved in hepatic lipoprotein synthesis. *In vitro* analysis, utilizing a transformed human liver (HepG-2) cell line, has demonstrated niacin’s ability to inhibit the DGAT2 enzyme, resulting in reduced hepatic TG synthesis and secretion (Ganji et al., 2004) (Fig. 1). Reduction in DGAT2 activity effectively reduces the supply of TG available for nascent apolipoprotein B (ApoB) particles, which may effectively increase intracellular degradation of ApoB and ultimately reduce ApoB containing particles such as very low density lipoproteins (VLDL) and Lp(a) (Fig. 1) (Guyton, 2004). VLDL formation is dependent upon hepatic TG construction, while intermediate density lipoprotein (IDL) and LDL synthesis are dependent upon the degree of VLDL formation. As a consequence of this sequential lipoprotein development, niacin therapy effectively impairs TG synthesis, leading to reduced levels of circulating VLDL, IDL, and LDL (Table 1) (Ganji et al., 2003; Zambon et al., 2014).

3.2. G Protein-coupled receptor activation

The niacin stimulation of anti-atherogenic pathways also involves direct activation of GPR109A (Kamanna and Kashyap, 2008), which has been proposed to have differential effects in various tissue types (Pike, 2005). In adipocytes, GPR109A activation can reduce intercellular cyclic adenosine monophosphate (cAMP) levels which control the activity of hormone sensitive lipase (HSL) (Fig. 2A) (Chow et al., 2008; Pike, 2005). As HSL inhibition occurs, a subsequent reduction in lipolysis and free fatty acid release occurs, resulting in reduced liver substrates