Journal of
Clinical and Experimental Pharmacology

Martin et al., Clin Exp Pharmacol 2013, S3
DOI: 10.4172/2161-1459.S3-003

Review Article Open Access

Expression of the Niacin Receptor GPR109A in Retina: More than Meets the Eye?

Pamela M Martin[1,2,4]*, Deeksha Gambhir[1], Wanwisa Promsote[1], Vadivel Ganapathy[1,4] and Debra Moore-Hill[3]

[1]*Departments of Biochemistry and Molecular Biology, Georgia Regents University, Augusta, USA*
[2]*Departments of Ophthalmology, Georgia Regents University, Augusta, USA*
[3]*Departments of Neurology, Georgia Regents University, Augusta, USA*
[4]*The James and Jean Culver Vision Discovery Institute, Georgia Regents University, Augusta, USA*

Abstract

GPR109A was discovered recently as the G-protein coupled receptor for niacin (nicotinic acid), a drug used widely in the treatment of hyperlipidemia. Upon its initial discovery, expression of the receptor was thought to be restricted primarily to adipocytes and immune cells (monocytes/macrophages), a pattern of localization consistent with the known actions of niacin – anti-lipolytic and anti-atherogenic. Of late however, several new reports have arisen detailing expression of the receptor in other cell and tissue types. Interestingly, with the exception of dermal Langerhans cells, the cells responsible for skin flushing, an unwanted side effect of high-dose niacin therapy, the function of the receptor in the additional cell types described is largely anti-inflammatory in nature. The receptor might also have a role in cancer; silencing of the receptor has been reported in colon and breast cancers, and forced expression of the receptor in tumor cells induces apoptosis, thereby suggesting a tumor-suppressive role for the receptor. This supports strongly not only the critical importance of GPR109A expression and activity under normal, basal conditions, but also the strength in impact that therapies capable of augmenting or optimizing its expression and activation may have in thwarting the development and progression of inflammation and cancer. Given the key causative role of inflammation in diabetic retinopathy, and the critical lack of viable strategies for intervening early in this pathology, new therapies, particularly those targeting inflammation, are sorely needed. Herein, we describe preclinical and clinical studies documenting the expression of GPR109A, the pleiotropic effects elicited in response to its activation and the underlying mechanisms to explain these actions. This information we discuss in the context of its relevance to diabetic retina, ultimately providing insight into strategy for future targeting of the receptor and development of new therapies for prevention and treatment of retinopathy in diabetes.

Keywords: Nicotinic acid; G-protein coupled receptor; GPR109A; Diabetes; Diabetic retinopathy; Retina; RPE

Introduction

Diabetic retinopathy (DR), one of the most common and feared complications of diabetes, is the leading cause of irreversible vision loss and blindness among adults of working-age in the U.S. and other industrialized countries [1,2]. The incidence of DR is high; nearly all type 1 patients and greater than 60 percent of patients with type 2 diabetes develop DR within the first 1-2 decades of their disease. In fact, at the time of diagnosis, signs of retinopathy are already detectable in many type 2 diabetic patients. Hyperglycemia is a primary factor in DR pathogenesis and while correcting it through maintenance of tight glycemic control (a task that is difficult in many patients) helps, it does not mitigate entirely DR development and progression [1,3]. There are at present treatments for DR (e.g., laser photocoagulation, vitrectomy, intravitreal anti-VEGF therapy); however in addition to being associated with adverse effects, these therapies are applicable only at the late stages of the disease when the signs and symptoms of proliferative microvascular disease present. But unfortunately, at these late stages, DR has already reached a relatively advanced state. Hence, there is a critical need for new, viable strategies for DR prevention and treatment.

Inflammation is implicated as a key causative factor both in the development and progression of DR [3-6]. Indeed, diabetes itself is recognized as a chronic, low-grade inflammatory disease. Congruent with this is a burgeoning literature suggesting strongly that therapies that reduce inflammation in retina may block early cellular and biochemical alterations in this tissue long before they become clinically evident. Thus, strategies to intervene within this "early" time frame have a high likelihood of effectively preventing or slowing progression of DR to advanced stage retinal disease and thereby, preserving vision and quality of life in a large number of persons. We identified recently in retina a new target, the G-protein coupled receptor GPR109A, that when activated therapeutically in diabetes could potentially fit this bill. In this short review, we discuss the clinical and experimental evidence that forms the basis of this rationale.

History of the Niacin Receptor, GPR109A

In 2003, GPR109A, also known as hydroxycarboxylic acid receptor 2 (HCA2) and formerly as HM74A in humans and PUMA-G (**P**rotein **U**pregulated in **MA**crophages by Interferon-**γ**) in rodents, was identified as the high-affinity receptor for niacin [7-10]. A second receptor with a high degree of homology to HM74A but a much lower affinity for niacin, HM74 (GPR109B), was also reported; however, its exact physiologic role remains unclear. Upon its initial discovery, GPR109A expression was thought to be limited primarily to adipocytes, the cell type in which the anti-lipolytic effects of niacin are most warranted. Niacin has been used widely to treat hyperlipidemia and remains today, five decades following its initial introduction, as one of the most effective agents for lowering low-density lipoprotein (LDL; "bad" cholesterol) and increasing High-Density Lipoprotein (HDL; "good"

***Corresponding author:** Pamela M Martin, Georgia Regents University, 1120 15th St., CN-1160, Augusta, GA 30912 USA, Tel: 706-721-4220; Fax: 706-721-6608; E-mail: pmmartin@gru.edu

Received April 04, 2013; **Accepted** April 27, 2013; **Published** April 29, 2013

Citation: Martin PM, Gambhir D, Promsote W, Ganapathy V, Moore-Hill D (2013) Expression of the Niacin Receptor GPR109A in Retina: More than Meets the Eye? Clin Exp Pharmacol S3:003. doi:10.4172/2161-1459.S3-003

cholesterol). In contrast, newer therapies such as HMG-CoA reductase inhibitors (statins) and fibric acid derivatives are effective only in reducing the LDL cholesterol [11,12]. Congruent with its improvement of lipid/lipoprotein characteristics, niacin is touted also for its ability to reduce vascular inflammation and thrombosis and therefore lower significantly the risk of atherosclerosis, stroke and other cardiovascular events, properties that we now know to be a direct consequence of its interaction with and subsequent activation of the G_i-protein coupled receptor GPR109A [13]. This entire highlighted sentence should be revised to read "The efficacy of niacin in slowing the progression of atherosclerosis and reducing cardiovascular events and mortality in patients with hyperlipidemia and the involvement of GPR109A in these actions is supported by a wealth of clinical and experimental evidence [14], though some recent studies have challenged these views.

Along with the identification of GPR109A as the receptor for niacin, came additional studies devoted to characterizing in detail the expression and function of the receptor in various cell and tissue types. Out of these studies came the identification of **β**-hydroxybutyrate and butyrate as endogenous receptor agonists [15,16], and importantly, the revelation that the benefits of activating the receptor therapeutically extend far beyond the alteration of lipid profiles [17,18]. In immune cells, cells central also to the development and progression of atherosclerotic lesions/cardiovascular disease, GPR109A activation was found to elicit robust anti-inflammatory responses by way of suppressed pro-inflammatory cytokine and chemokine expression and signaling [19]. The same anti-inflammatory effect was described also in adipocytes [20]. Additional studies involving mouse and human endothelial cells demonstrated the potentiation of responses that were both antioxidant and anti-inflammatory in nature in association with GPR109A activation [11,21,22]. Investigations into the role of the receptor under normal physiologic conditions and the consequences of its activation by endogenous ligands (e.g., **β**-hydroxybutyrate, butyrate), which happen to be intermediates of normal metabolism, led to the discovery of a role for the receptor also in nutrient sensing and energy regulation, and in tumor suppression [17,23,24].

GPR109A Expression in Retina and Rationale for Therapeutic Targeting in Diabetes

As detailed above, the major cellular properties attributed to GPR109A-dependent signaling to date can be described in sum as: lipid-modulatory, anti-inflammatory, anti-oxidative, and energy regulating. The underlying molecular mechanisms to explain these actions include regulation of the activity of lipolytic enzymes (i.e., hormone-sensitive lipase in adipocytes) and cholesterol efflux transport proteins [7-10,15,25]; suppression of Nuclear Factor Kappa-B (NF-kB) signaling [16]; Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-**γ**) activation [26]; and regulation of monocarboxylate transporter expression and functional activity [24]. Alone, each of the aforementioned responses is highly desirable in diabetic retina; however, the discovery of a single receptor with the potential to influence them collectively is extremely significant with respect to developing new, targeted therapies for DR prevention and treatment.

The involvement of inflammation and oxidative stress in DR pathogenesis is undeniable. While there are conflicting opinions as to the existence of a concrete link between atherosclerosis/cardiovascular disease, the pathology for which therapeutic intervention via GPR109A activation is most noted, and DR incidence and severity [27], clinical and experimental evidences support overwhelmingly a definitive correlation between the two [28,29]. Hence, enthusiasm in this regard is in no way diminished. Indeed, altered lipid metabolism and lipoprotein abnormalities are not only well established features of diabetes but more specifically, of diabetic retina. Hypertriglyceridemia is common in type 1 diabetes and even more so in type 2 diabetes, with type 2 patients commonly presenting with reduced HDL-choleserol levels in addition to hypertriglyceridemia [30]. In retina specifically, the size and density of hard exudates in diabetic patients is thought to be reflective directly of the severity of alteration in retinal lipid profiles [31,32]. Whether patients under niacin therapy suffer less by diabetic retinopathy has not been evaluated specifically. However, fibrates and statins, well-known anti-hyperlipidemic agents, have been shown to reduce significantly the risk of advanced DR development and progression both in human patients and experimental models of disease [31-35]. There are an increasing number of new reports citing the benefits of niacin-GPR109A signaling in the treatment of pathologies other than hyperlipidemia (e.g., multiple sclerosis, septic shock, lung inflammation and fibrosis, renal failure, ischemia-induced neovascularization and peripheral vascular dysfunction in diabetes) [36-40]. This coupled with the fact that niacin, the prototypic GPR109A agonist, elicits additional, unique actions atop its lipid-lowering effects via its interaction with GPR109A raises the question as to whether similar or added benefit might be attained upon therapeutic targeting of the receptor in DR. This is a question well worthy of investigation. However, before progress can be made toward addressing this issue, the expression of GPR109A in retinal cell types and intact retina must be characterized fully and its functional significance therein elucidated.

Along these lines, in 2009, we reported for the first time ever, expression of GPR109A in retina [41]. Evaluation of cross sections of mouse retina and transformed human and rodent retinal cell lines revealed the localization of the receptor in Retinal Pigmented Epithelium (RPE) and more specifically, to the basolateral membrane of this cellular layer. This localization is ideally suited for interaction of the receptor with ligands, endogenous or pharmacologic, presenting from the choroidal circulation. Our subsequent inquiry into the functional significance of RPE-specific GPR109A expression led to the discovery of a potent role for the receptor upon its activation by exogenous niacin or **β**-hydroxybutyrate in the mediation of anti-inflammatory signaling not only in cultured RPE cells [42], but also in intact mouse retina as evidenced by the suppressed expression (mRNA and protein) of pro-inflammatory molecules such as Interleukin-1**β** (IL-1**β**), Monocyte Chemotactic Protein-1 (MCP-1), Intercellular Adhesion Molecule-1 (ICAM-1) and, the reduction of other notable hallmarks of retinal inflammation such as increased leukostasis (unpublished results). Further investigation into the effects of diabetes on receptor expression led to the revelation that not only does retinal expression of GPR109A persist in diabetes (both type 1 and type 2 diabetes - determined by analysis of receptor expression in post-mortem human retina and in rodent models of diabetes) but, that it appears to be upregulated in this condition [42]. While this confirms the presence and availability of the receptor for targeting in diabetic retina, the functional significance of its upregulation remains to be determined. We postulate that it represents a mechanism by which the tissue tries to stop the progression of the damage caused by the disease, one precluded by the absence of an endogenous agonist present at levels sufficient to augment maximally the beneficial effects of GPR109A signaling. In healthy individuals, **β**-hydroxybutyrate, a principal ketone and physiologic GPR109A agonist, is present in the circulation, but at a relatively low concentration, increasing only slightly during periods of fasting or prolonged exercise. Ketone bodies serve as alternate sources of energy to maintain crucial organs such as the brain, retina, heart,

kidney cortex and skeletal muscle when carbohydrates are either in short supply or as is the case in diabetes, cannot be used effectively [43]. Hence, in well-controlled diabetes, significant increases in circulating **β**-hydroxybutyrate do not occur. Though seemingly protective in moderation, when elevated excessively, as in uncontrolled diabetes, the effects of **β**-hydroxybutyrate are thought to be largely detrimental (e.g., ketoacidosis). This suggests that despite the presence of both the receptor and the agonist in such conditions, activation of the receptor may not occur at the optimal level and hence the beneficial effects of receptor signaling are lost. It is also plausible, particularly at such high concentrations, that additional, GPR109A-independent mechanisms come in to play. Thus, if receptor activation can be augmented optimally through the use of pharmacological agonists, robust benefits may be reaped in diabetic retina. Support for this line of thought and therefore the therapeutic targeting of GPR109A in diabetic retina can be inferred from the recent report by Poplawski et al. [44] demonstrating pronounced and effective reversal of parameters associated with progression and increased severity of diabetic nephropathy, another major complication of diabetes, through employment of a ketogenic diet, a diet in which **β**-hydroxybutyrate is the predominant ketone. Additional support can be gathered from a study by Huang et al. [40] in which the authors report niacin-induced improvement of blood flow and peripheral vascular function in a diabetic rodent model of ischemia-reperfusion through mechanisms involving the modification of nitric oxide bioavailability and reduction of oxidative stress, and from clinical and experimental studies of neurodegenerative brain diseases touting the cellular protective effects of **β**-hydroxybutyrate when employed therapeutically [45].

Inflammation and reactive oxygen species production are normal physiologic processes. Inflammation is essential to cellular defense, repair and turnover and reactive oxygen species are produced normally as a consequence or byproduct of many normal biologic processes. Therefore, cells, including those of the retina, are naturally equipped to deal with these factors, as they must on a regular basis, in order to maintain tissue homeostasis. In pathologic conditions such as diabetes and DR however, the increased production pro-inflammatory and pro-oxidant factors coupled with the decrease in the cellular defense machinery, influences negatively the delicate balance between pro-inflammatory/pro-oxidant and anti-inflammatory/antioxidant factors; this has been documented and described on numerous occasions [4,5,46,47]. Therefore, could it be that when elevated in moderation, **β**-hydroxybutyrate activates GPR109A expressed by neurons, RPE, and other cell types, thereby conferring protection against inflammation, oxidative stress and other types of cellular insult but, in extreme excess (i.e., ketoacidosis) it tips the scale in the opposite direction, favoring increased inflammation, oxidative stress and cellular damage? The likelihood of an affirmative answer to this question is strengthened by the fact that niacin, when taken at lower doses (< 1 g daily) has proven to be quite effective at improving lipid profiles and reducing the risk of atherosclerosis and cardiovascular disease development and progression in a large number of patients; however, when given at very high doses (3.0 – 4.5 g daily), use of the compound, while still effective in the aforementioned parameters, is associated with three major side effects [11]. The first is flushing, an effect that we now know to be due to the unwanted effects of this compound/GPR109A activation in dermal Langerhans and keratinocytes [48]. The second and third, respectively, are a reversible form of cystoid maculopathy (occurs only in 0.67% of patients), and modest hyperglycemia [11,49]. These undesirable effects have fueled the search for lipid-lowering therapies in lieu of niacin. However, of the alternative therapies discovered and employed, the fact remains that none have proven to be as effective as niacin at raising HDL levels and improving additional parameters consistent with reduced risk of advanced cardiovascular disease; for this primary reason, the clinical use of niacin has continually been revisited. Indeed, the recent introduction of immediate-release and extended-release forms of the niacin brings the compound back to the forefront as the incidence and severity of the adverse effects associated with its use has been reduced significantly even when the agent is employed at very high doses while retaining the benefits attributed to the original compound [11]. Of specific interest and relevance to our present topic, the potential employment of GPR109A agonists for therapeutic management of DR, is the fact that the incidence of ocular side effects (niacin maculopathy), which was already relatively low, appears to have diminished even further as evidenced by the few, rare reports that can be found in the published literature over the past decade. The same is true with respect to niacin-induced deterioration of glycemic control in diabetic patients, which is now reported as being only minor with no evidence of increased incidence of new onset diabetes [11,50]. Furthermore, the avoidance or lessening of the flushing response is important, as it may impact positively patient compliance rates. The discovery by Walters et al. [51] that niacin-induced signaling through beta-arrestin 1 is responsible for flushing but not for the anti-lipolytic effects of the compound suggests that relevant compounds that activate GPR109A in a beta-arrestin-independent fashion could be developed. Hence, targeting GPR109A for therapeutic management of DR, whether by the use of niacin, other newly identified pharmacologic ligands like monomethylfumarate [49,52] or alternately, intake of a ketogenic diet to increase the endogenous agonist **β**-hydroxybutyrate, remains as a feasible and seemingly viable option that should be explored further. The appeal for such is heightened by the fact that it might be accomplished successfully via the re-purposing of existing compounds or strategies that have already garnered FDA-approval for treatment of other indications and therefore much is known regarding the toxicological and pharmacokinetic properties in humans.

The demonstration of GPR109A expression in RPE and its function there in modulating inflammation is a novel and important finding. RPE facilitates numerous functions that are critically essential to retinal health and visual function normally and in diabetes including the regulation of immunity and inflammation in the outer retina via the expression and secretion of a plethora of cytokines and chemokines, maintenance of outer-blood retinal barrier integrity, phagocytosis of shed photoreceptor discs, cholesterol transport/lipid homeostasis, light absorption, amino acid and nutrient transport, etc. [53,54]. However, it is clear that in DR other retinal cell types are largely affected [55]. There are a number of studies suggesting strongly that processes similar to those that promote and/or potentiate atherosclerogenesis occur also in diabetic retina [56,57]. A role for inflammation and oxidative stress in DR has been established. Atop this are clinical studies demonstrating retinal dysfunction and cellular damage in association with lipid accumulation in this tissue [31,32,58] and experimental studies demonstrating the critical causative role of dyslipidemia in endothelial cell dysfunction and vascular inflammation in retina [59]. Could GPR109A in retina be expressed by retinal cell types in addition to RPE, and upon activation therein contribute to the propagation of multiple, unique responses that are, like the demonstrated actions associated with GPR109A expressed in other organs, overwhelmingly beneficial (i.e., improved retinal lipid profiles, reduced inflammation and oxidative stress, protected and preserved retinal cell viability and vascular integrity/function)? Along these lines, our group has initiated additional studies. Using primary rat microglial cells isolated following

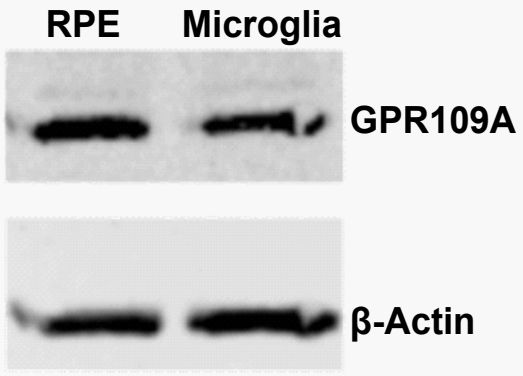

Figure 1: GPR109A expression in rat retinal microglia. Western blot analysis of GPR109A expression in primary retinal microglial cells isolated from rat retina. Protein isolated from primary mouse Retinal Pigment Epithelial Cells (RPE) was included as a positive control for GPR109A expression. β-Actin served as the loading control.

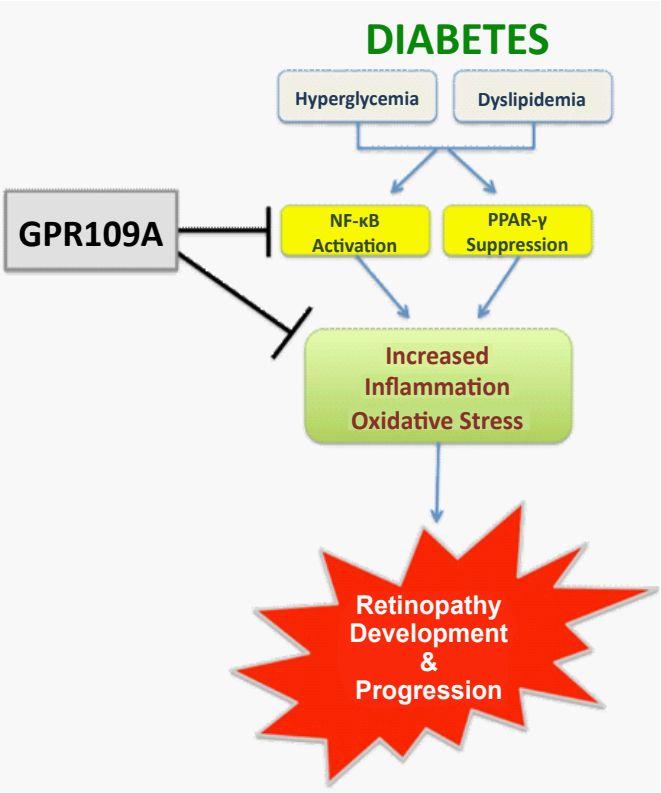

Figure 2: Hypothetical model for therapeutic intervention in diabetic retinopathy via augmentation of GPR109A signaling. Hyperglycemia and dyslipidemia are major features of diabetes and are known to potentiate factors that contribute to the increased oxidative stress and inflammation characteristic of the disease. Of those factors, clinical and experimental studies show upregulated Nuclear Factor-kappa B (NF-kB) and reduced Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ) activity to be crucial. Studies conducted using non-retinal cells and tissues show GPR109A to be effective at reversing and/or inhibiting these parameters upon its activation by specific agonists. Additionally, GPR109A may elicit other direct effects congruent with reduced inflammation and oxidative stress. In retina, GPR109A is expressed in cells critical to the regulation of tissue immunity and inflammation (e.g., Retinal Pigment Epithelial (RPE) and microglia) and similarly suppresses inflammation and oxidative stress when activated. Thus, therapies to augment this phenomenon in diabetic retina may prevent or delay the development and progression of retinopathy.

the method of Roque and Caldwell [60], a generous gift from the laboratory of Dr. Gregory Liou (Georgia Regents University, Augusta, GA), and our rabbit polyclonal GPR109A antibody [41], we evaluated GPR109A expression by Western blotting techniques per our published method [61] (Figure 1). Protein extracted from primary RPE cells that were isolated from normal mouse retinas as described previously [41] was included as a positive control. Microglia are in essence the resident macrophage cells of the retina; their critical involvement in potentiating inflammation and therefore the development and progression of diabetic retinopathy is well documented [62-64]. Our studies have shown that microglia express GPR109A robustly. Though novel, the finding of GPR109A expression in these cells did not come as a surprise given the original description of the receptor protein as PUMA-G (protein-upregulated in macrophages by interferon-γ) and the well established role of these cells in the mediation of inflammatory processes in retina. However, additional studies to ascertain fully the functional significance of GPR109A expression and activation in this retinal cell type normally and in diabetes are needed. Similar studies are also needed with retinal endothelial cells; our preliminary work in this regard leads us to believe that the consequences of GPR109A activation in these cells will be, as described for peripheral vascular endothelial cells, largely anti-inflammatory.

Conclusions

Based on existing clinical and experimental evidence and our own published and preliminary findings, we speculate that GPR109A expression in retina is essential to the normal regulation of multiple parameters, both lipid-dependent and lipid-independent (e.g., inflammation, the metabolism and handling of lipids, nutrient sensing and energy regulation). Hence, therapies to target this receptor in diabetes may be effective in preventing or slowing the development and progression of DR (Figure 2). Additionally, there is the promise that such strategies could be of benefit also in the prevention and treatment of other debilitating retinal diseases in which inflammation, oxidative stress and/or altered lipid regulation are majorly involved such as for example, age-related macular degeneration.

References

1. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, et al. American Diabetes Association. Retinopathy in diabetes. Diabetes Care 27: S84-S87.
2. Klein R, Klein BE, Moss SE, Cruickshanks KJ (1994) The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. Arch Ophthalmol 112: 1217-1228.
3. Antonetti DA, Barber AJ, Bronson SK, Freeman WM, Gardner TW et al. (2006) For the JDRF Diabetic Retinopathy Center Group. Diabetic retinopathy: Seeining beyond glucose-induced microvascular disease. Diabetes 55: 2401-2411.
4. Tang J, Kern TS (2011) Inflammation in diabetic retinopathy. Prog Retin Eye Res 30: 343-358.
5. Zhang W, Liu H, Rojas M, Caldwell RW, Caldwell RB (2011) Anti-inflammatory therapy for diabetic retinopathy. Immunotherapy 3: 609-628.
6. Gologorsky D, Thanos A, Vavvas D (2012) Therapeutic interventions against inflammatory and angiogenic mediators in proliferative diabetic retinopathy. Mediators Inflamm 2012: 629452.
7. Tunaru S, Kero J, Schaub A, Wufka C, Blaukat A, et al. (2003) PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. Nat Med 9: 352-355.
8. Wise A, Foord SM, Fraser NJ Barnes AA, Elshourbagy N, Eilert M, et al. (2003) Molecular identification of high and low affinity receptors for nicotinic acid. J Biol Chem 278: 9869-9874.
9. Soga T, Kamohara M, Takasaki J, Matsumoto S, Saito T, (2003) Molecular

identification of the nicotinic acid receptor. Biochem Biophys Res Commun 303: 364-369.

10. Offermanns S, Colletti SL, Lovenberg TW, Semple G, Wise A, et al. (2011) International Union of Basic and Clinical Pharmacology. LXXXII: Nomenclature and Classification of Hydroxy-carboxylic Acid Receptors (GPR81, GPR109A, and GPR109B). Pharmacol Rev 63: 269-290.
11. Guyton JR (2007) Niacin in cardiovascular prevention: mechanisms, efficacy, and safety. Curr Opin Lipidol 18: 415-420.
12. Safeer RS, Lacivita CL (2000) Choosing drug therapy for patients with hyperlipidemia. Am Fam Physician 61: 3371-3382.
13. Keener A, Sanossian N (2008) Niacin for stroke prevention: evidence and rationale. CNS Neurosci Ther 14: 287-294.
14. Meyers CD, Kamanna VS, Kashyap ML (2004) Niacin therapy in atherosclerosis. Curr Opin Lipidol 15: 659-665.
15. Taggart AK, Kero J, Gan X, Cai TQ, Cheng K, et al. (2005) (D)-beta-Hydroxybutyrate inhibits adipocyte lipolysis via the nicotinic acid receptor PUMA-G. J Biol Chem 280: 26649-26652.
16. Thangaraju M, Cresci GA, Liu K, Ananth S, Gnanaprakasam JP, et al. (2009) GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. Cancer Res 69: 2826-2832.
17. Blad CC, Tang C, Offermanns S (2012) G protein-coupled receptors for energy metabolites as new therapeutic targets. Nat Rev Drug Discov 11: 603-619.
18. Chai JT, Digby JE, Choudhury RP (2013) GPR109A and Vascular Inflammation. Curr Atheroscler Rep 15: 325.
19. Digby JE, Martinez F, Jefferson A, Ruparelia N, Chai J, et al. (2012) Anti-inflammatory effects of nicotinic acid in human monocytes are mediated by GPR109A dependent mechanisms. Arterioscler Thromb Vasc Biol 32: 669-676.
20. Digby JE, McNeill E, Dyar OJ, Lam V, Greaves DR, et al. (2010) Anti-inflammatory effects of nicotinic acid in adipocytes demonstrated by suppression of fractalkine, RANTES, and MCP-1 and upregulation of adiponectin. Atherosclerosis 209: 89-95.
21. Ganji SH, Qin S, Zhang L, Kamanna VS, Kashyap ML (2009) Niacin inhibits vascular oxidative stress, redox-sensitive genes, and monocyte adhesion to human aortic endothelial cells. Atherosclerosis 202: 68-75.
22. Digby JE, Ruparelia N, Choudhury RP (2012) Niacin in cardiovascular disease: recent preclinical and clinical developments. Arterioscler Thromb Vasc Biol 32: 582-588.
23. Tao YX, Yuan ZH, Xie J (2013) G protein-coupled receptors as regulators of energy homeostasis. Prog Mol Biol Transl Sci 114: 1-43.
24. Borthakur A, Priyamvada S, Kumar A, Natarajan AA, Gill RK, et al. (2012) A novel nutrient sensing mechanism underlies substrate-induced regulation of monocarboxylate transporter-1. Am J Physiol Gastrointest Liver Physiol 303: G1126-G1133.
25. Li X, Millar JS, Brownell N, Briand F, Rader DJ (2010) Modulation of HDL metabolism by the niacin receptor GPR109A in mouse hepatocytes. Biochem Pharmacol 80: 1450-1457.
26. Knowles HJ, te Poele RH, Workman P, Harris AL (2006) Niacin induces PPARgamma expression and transcriptional activation in macrophages via HM74 and HM74a-mediated induction of prostaglandin synthesis pathways. Biochem Pharmacol 71: 646-656.
27. Lim LS, Wong TY (2012) Lipids and diabetic retinopathy. Expert Opin Biol Ther 12: 93-105.
28. van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, et al. (2002) Blood pressure, lipids, and obesity are associated with retinopathy: the hoorn study. Diabetes Care 25: 1320-1325.
29. Tedeschi-Reiner E, Reiner Z, Sonicki Z (2004) Atherosclerosis of retinal arteries in men: role of serum lipoproteins and apoproteins. Croat Med J 45: 333-337.
30. O'Brien T, Nguyen TT, Zimmerman BR (1998) Hyperlipidemia and diabetes mellitus. Mayo Clin Proc 73: 969-976.
31. Ferris FL 3rd, Chew EY, Hoogwerf BJ (1996) Serum lipids and diabetic retinopathy. Early Treatment Diabetic Retinopathy Study Research Group. Diabetes Care 19: 1291-1293.
32. Chew EY, Klein ML, Ferris FL 3rd, Remaley NA, Murphy RP, et al. (1996) Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. Arch Ophthalmol 114: 1079-1084.
33. Simó R, Hernández C (2012) Prevention and treatment of diabetic retinopathy: evidence from large, randomized trials. The emerging role of fenofibrate. Rev Recent Clin Trials 7: 71-80.
34. Ansquer JC, Crimet D, Foucher C (2011) Fibrates and statins in the treatment of diabetic retinopathy. Curr Pharm Biotechnol 12: 396-405.
35. Wong TY, Simó R, Mitchell P (2012) Fenofibrate - a potential systemic treatment for diabetic retinopathy? Am J Ophthalmol 154: 6-12.
36. Penberthy WT (2009) Nicotinic acid-mediated activation of both membrane and nuclear receptors towards therapeutic glucocorticoid mimetics for treating multiple sclerosis. PPAR Res 2009: 853707.
37. Kapoor A, Thiemermann C (2011) Niacin as a novel therapy for septic shock? Crit Care Med 39: 410-411.
38. Kwon WY, Suh GJ, Kim KS, Kwak YH (2011) Niacin attenuates lung inflammation and improves survival during sepsis by downregulating the nuclear factor-ÎºB pathway. Crit Care Med 39: 328-334.
39. Cho KH, Kim HJ, Rodriguez-Iturbe B, Vaziri ND (2009) Niacin ameliorates oxidative stress, inflammation, proteinuria, and hypertension in rats with chronic renal failure. Am J Physiol Renal Physiol 297: F106-113.
40. Huang PH, Lin CP, Wang CH, Chiang CH, Tsai HY, et al. (2012) Niacin improves ischemia-induced neovascularization in diabetic mice by enhancement of endothelial progenitor cell functions independent of changes in plasma lipids. Angiogenesis 15: 377-389.
41. Martin PM, Ananth S, Cresci G, Roon P, Smith S, et al. (2009) Expression and localization of GPR109A (PUMA-G/HM74A) mRNA and protein in mammalian retinal pigment epithelium. Mol Vis 15: 362-372.
42. Gambhir D, Ananth S, Veeranan-Karmegam R, Elangovan S, Hester S, et al. (2012) GPR109A as an anti-inflammatory receptor in retinal pigment epithelial cells and its relevance to diabetic retinopathy. Invest Ophthalmol Vis Sci 53: 2208-2217.
43. Laffel L (1999) Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev 15: 412-426.
44. Poplawski MM, Mastaitis JW, Isoda F, Grosjean F, Zheng F, et al. (2011) Reversal of diabetic nephropathy by a ketogenic diet. PLoS One 6: e18604.
45. Gasior M, Rogawski MA, Hartman AL (2006) Neuroprotective and disease-modifying effects of the ketogenic diet. Behav Pharmacol 17: 431-439.
46. Roy S, Trudeau K, Roy S, Tien T, Barrette KF (2012) Mitochondrial Dysfunction and Endoplasmic Reticulum Stress in Diabetic Retinopathy: A Mechanistic Insight for High Glucose-Induced Retinal Cell Death. Curr Clin Pharmacol.
47. Santos JM, Mohammad G, Zhong Q, Kowluru RA (2011) Diabetic retinopathy, superoxide damage and antioxidants. Curr Pharm Biotechnol 12: 352-361.
48. Hanson J, Gille A, Zwykiel S, Lukasova M, Clausen BE, et al. (2010) Nicotinic acid- and monomethyl fumarate-induced flushing involves GPR109A expressed by keratinocytes and COX-2 dependent prostanoid formation in mice. J Clin Invest 120: 2910-2919.
49. Millay RH, Klein ML, Illingworth DR (1988) Niacin maculopathy. Ophthalmology 95: 930-936.
50. Sazonov V, Maccubbin D, Sisk CM, Canner PL (2013) Effects of niacin on the incidence of new onset diabetes and cardiovascular events in patients with normoglycaemia and impaired fasting glucose. Int J Clin Pract 67: 297-302.
51. Walters RW, Shukla AK, Kovacs JJ, Violin JD, DeWire SM, et al. (2009) beta-Arrestin1 mediates nicotinic acid-induced flushing, but not its antilipolytic effect, in mice. J Clin Invest 119: 1312-1321.
52. Tang H, Lu JY, Zheng X, Yang Y, Reagan JD (2008) The psoriasis drug monomethylfumarate is a potent nicotinic acid receptor agonist. Biochem Biophys Res Commun 375: 562-565.
53. Sparrow JR, Hicks D, Hamel CP (2010) The retinal pigment epithelium in health and disease. Curr Mol Med 10: 802-823.
54. Simó R, Villarroel M, Corraliza L, Hernández C, Garcia-Ramírez M (2010) The retinal pigment epithelium: something more than a constituent of the blood-

retinal barrier--implications for the pathogenesis of diabetic retinopathy. J Biomed Biotechnol 2010: 190724.

55. Tarr JM, Kaul K, Wolanska K, Kohner EM, Chibber R (2012) Retinopathy in diabetes. Adv Exp Med Biol 771: 88-106.

56. Arcidiacono MV, Traveset A, Rubinat E, Ortega E, Betriu A, et al. (2013) Microangiopathy of large artery wall: A neglected complication of diabetes mellitus. Atherosclerosis.

57. Ellis TP, Choudhury RH, Kaul K, Chopra M, Kohner EM, et al. (2013) Diabetic retinopathy and atherosclerosis: is there a link? Curr Diabetes Rev 9: 146-160.

58. Chew EY (1997) Diabetic retinopathy and lipid abnormalities. Curr Opin Ophthalmol 8: 59-62.

59. Chen W, Jump DB, Grant MB, Esselman WJ, Busik JV (2003) Dyslipidemia, but not hyperglycemia, induces inflammatory adhesion molecules in human retinal vascular endothelial cells. Invest Ophthalmol Vis Sci 44: 5016-5022.

60. Roque RS, Caldwell RB (1993) Isolation and culture of retinal microglia. Curr Eye Res 12: 285-290.

61. Ananth S, Babu E, Veeranan-Karmegam R, Bozard Baldowski BR, Boettger T, et al. (2013) Induction of the cystine/glutamate exchanger SLC7A11 in retinal pigment epithelial cells by the antipsoriatic drug monomethylfumarate. Invest Ophthalmol Vis Sci 54: 1592-1602.

62. Chen L, Yang P, Kijlstra A (2002) Distribution, markers, and functions of retinal microglia. Ocul Immunol Inflamm 10: 27-39.

63. Malchiodi-Albedi F, Matteucci A, Bernardo A, Minghetti L (2008) PPAR-gamma, Microglial Cells, and Ocular Inflammation: New Venues for Potential Therapeutic Approaches. PPAR Res 2008: 295784.

64. Coorey NJ, Shen W, Chung SH, Zhu L, Gillies MC (2012) The role of glia in retinal vascular disease. Clin Exp Optom 95: 266-281.

This article was originally published in a special issue, **Signaling Pathways in Functional Cells** handled by Editor(s). Dr. Li-Na Wei, University of Minnesota, USA