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Editorial

New intercellular lipid mediators and their GPCRs: An update

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ABSTRACT

Intercellular lipid mediators such as prostaglandins and lysophosphatidic acid (LPA) interact with their G-protein-coupled receptors (GPCR) in the plasma membrane to modulate functions of target cells or tissues. Discovery of new members of intercellular lipid mediators and their GPCRs have been milestones in lipid biology and the foundation for drug development. Recent advances in intercellular lipid mediators are very interesting. New lipid molecules have been recognized as intercellular signaling mediators acting on GPCRs including resolvin E1, eoxin, acylethanolamides (arachidnonylethanolamide and oleoylethanolamide), fatty acids, bile acids, lipoamino aicd (N-palmitoyl glycine and N-arachidonyl glycine), estrogen, 5-oxo-ETE and 9-hydroxyoctadecadienoic acid, among others. Also new GPCRs for LPA have been identified. New intercellular lipid mediators and their GPCRs are reviewed.

1. Introduction to intercellular lipid mediators and GPCRs

Intercellular lipid mediators are hormone-like signaling molecules with a lipid structure, in contrast to intracellular lipid mediators such as second messengers of diacylglycerol (DAG) or phosphatidylinositol 3,4,5-trisphosphate (PIP_3) [1]. There are two groups of intercellular lipid mediators: one has their receptors in the plasma membrane and the other has intracellular nuclear receptors such as corticosteroids [1]. A number of intercellular lipid mediators act on G-protein-coupled receptors (GPCR) such as prostaglandins and lysophospholipids in the plasma membrane.

Recent findings suggest that some lipid mediators have two types of receptors, GPCR and nuclear receptors. For example, estrogen and bile acids have been recognized to act not only through their nuclear receptors, estrogen receptor (ER) and farnesoid X receptor (FXR) but also through GPCRs, GPR30 for estrogen and TGR5/BG37 for bile acids [2–5]. On the other hand, lysophosphatidic acid (LPA), which acts on five or more GPCRs (LPA_{1-5}) in the plasma membrane, could also act on a nuclear receptor, peroxisome proliferation-activating receptor (PPARγ) [6,7]. The present introductory review will, however, only focus on intercellular lipid mediators acting on GPCRs since these are the most attractive targets for the development of new therapeutics [8]. A variety of GPCRs (approximately 376) give chances of drug selectivity to receptor-selective agonists and antagonists [9,10]. In practice, almost a half of the medications in the market act positively or negatively on GPCRs. Among GPCR ligands, lipid mediators compose a small group but have made substantial contribution to medical science proved by prostaglandins and aspirin [1,11].

Novel lipid mediators and GPCRs have been reviewed previously [1,9,11–14]. Recent advances in this field, however, compelled the organization of a special issue on "Intercellular Lipid Mediators and Their GPCRs" in Prostaglandins and Other Lipid Mediators. This mini-review will introduce recent advances in intercellular lipid mediators and their GPCRs. The special issue will cover selected topics concisely among the recent advances. For readers interested in other topics that are not covered in the special issue, the author recommends checking the original or reviewed articles [15–20].

2. Recent advances in intercellular lipid mediators and GPCRs

2.1. GPCRs for lysophospholipids

Since the cloning of the cannabinoid receptor in 1990, many GPCRs for intercellular lipid mediators were cloned, such as GPCRs for platelet-activating factor, prostaglandins, leukotrienes, LPA, and sphingosine 1-phosphate (S1P) [11,21–24]. From 2000 the OGR1 subfamily of GPCRs (OGR1/GPR68, GPR4, TDAG8/GPR65, and G2A/GPR132) were matched with sphingosylphosphorylcholine (SPC), lysophosphatidylcholine (LPC) and psychosine [25]. Later, those GPCRs were reported as proton-sensing GPCRs [25,26]. Original reports for OGR1, GPR4, and G2A as lysolipid receptors were retracted later. Although antagonistic and agonistic effects of lysolipids on those GPCRs have been reported [27–35], pathophysiological roles of those GPCRs as pH sensors have been intensively studied and widely supported [36–43].

Recently, Izumi's group reported 9-hydroxyoctadecadienoic acid as a ligand for G2A/GPR132 [44]. This will be reviewed in the present issue [45]. Kabarowski also review on G2A and LPC in immune regulation [46]. GPR3, GPR6 and GPR12 were first reported as adenylyl cyclase-activating orphan GPCRs [47]. In 2002, Kostenis's group reported them as additional GPCRs for S1P [48] and another group reported GPR6 as an S1P receptor and GPR12 as an SPC receptor [49,50]. Later, the constitutive activation of Gs proteins by GPR3 and its role in the meiotic prophase arrest of oocytes with antral follicles were demonstrated with GPR3-knockout mice, although supportive evidence for the S1P ligand matching was poorly provided [48,51–54]. GPR23/LPA_4, GPR92/LPA_5, P2Y5, and GPR87 were reported as additional members of LPA receptors

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[55–60], although GPR92/LPA_5 was recently reported as a receptor for farnesyl pyrophosphate and N-arachidonylglycine [61]. Ishii will review the advances on this topic [62].

GPR40, GPR41, GPR43 and GPR120 have been recognized as GPCRs for short chain and medium long chain fatty acids [63–68]. The regulation of secretion of glucagon-like peptide-1 and insulin by free fatty acids through GPR120 and GPR40 is crucial in the treatment of diabetes. Tsujimoto's review on this topic will be helpful for interested readers [69]. GPR63 was reported as a GPCR recognizing S1P and dioleoyl phosphatidic acid [70], but no other supporting reports have been published as yet. Lysophosphatidylserine (LPS), an activator of mast cell degranulation, was identified as a ligand for GPR34, which is highly expressed in mast cells [71]. This topic will be covered by Aoki including recent advances on lysophosphatidylthreonine, lysophosphatidylethanolamine and lysophosphatidylglycerol [72–74].

2.2. GPCRs for endogenous acylethanolamides: GPR55 for anadamide/lysophosphstidylinositol and GPR119 oleoyethanolamide/lysophosphatidylcholine

Additional cannabinoid receptors, in addition to CB_1 and CB_2 classical cannabinoid receptors, have been implicated in studies with $CB_1^{-/-}$ and $CB_2^{-/-}$ knock-out mice and natural and synthetic cannabinoid mimetic chemicals. Starting from patent applications, several groups reported that GPR55 was the cannabinoid receptor, although it was phylogenetically distant from CB_1 and CB_2 receptors [75–77]. However, Sugiura's group was unable able to reproduce this result and instead suggested lysophosphatidylinositol (LPI, 2-arachidonyl-*sn*-glycero-3-phosphate) as a ligand [78,79]. So far, 6 papers have reported GPR55 as an atypical cannabinoid receptor and its signaling [76,77,80–82]. Among these, 3 studies confirmed that LPI could act as an agonist for GPR55 [76,77,80–82]. One particular study supported LPI as a ligand and failed to observe positive activation of GPR55 with cannabinoids, but they observed agonism with a cannabinoid antagonist, AM251 [83]. Based on multiple confirmations, it likely appears that GPR55 is an additional member of the cannabinoid receptor family and could also be modulated by LPI. A recent report interestingly suggested a cross modulation between CB receptor and GPR55 by integrin-clustering in endothelial cells [80]. Kunos's review would be more precise on this issue [84].

GPR119 was first reported as a receptor for lysophosphatidylcholine, which enhanced glucose-induced insulin secretion [85]. Acylethanolamides including oleoylethanolamide (OEA), palmitoylethanolamide and stearoylethanolamide, were shown to activate GPR119 more potently than LPC [86]. Furthermore, its hypophagic effect (reduction of food intake) has been a focus of anti-diabetic drug development [87]. Considering that arachidonylethanolamine (also known as anandamide) is an endogenous ligand for GPR55 along with oleoylethanolamide for GPR119, acylethanolamides could be a sub-group of ligands for GPCR [88].

2.3. GPCRs for eicosatetraenoic acids, bile acids and estrogen

A GPCR termed as TG1019, R527 or hGPCR48 was cloned and shown to recognize eicosatetraenoic acids and polyunsaturated fatty acids, including 5-oxo-6E, 8Z, 11Z, 14Z-eicosatetraenoic acid (5-oxo-ETE) [89,90]. The most potent agonist, 5-oxo-ETE, has long been known as a potent chemotactic factor for eosinophils and neutrophils [89,90]. Signaling pathways for the chemotaxis response has been studied [91,92]. Based on the structure-activity data, IUPHAR Nomenclature Committee renamed it as an oxoeicosanoid (OXE) receptor, because 5-oxo-ETE, is the most potent agonist in the cloned receptor assays and the oxo group at C-5 is key for activation of this receptor [93]. Powell will review on this topic [94,95].

Bile acids have long been known to be essential in dietary lipid absorption and cholesterol catabolism [96]. Recently, bile acids are increasingly being appreciated as complex metabolic integrators and signaling factors [97]. TGR5 also known as Gpbar1 was identified as a receptor for bile acids [3,4]. Although bile acids signal through nuclear hormone receptors such as farnesoid X receptor α (FXR-α), GPCR-mediated responses of bile acids are distinguishable from the nuclear receptor-mediated responses. It was shown that administration of bile acids to mice increased energy expenditure in brown adipose tissue, preventing obesity and resistance to insulin [96]. Such a metabolic effect of bile acids is mediated through TGR5 activation, cAMP production, and subsequent activation of protein kinase A in white adipose tissue in mouse and in skeletal muscle in human. PKA activation induces induction of thyroid hormone activating enzyme type 2 iodothyronine deiodinase, resulting in conversion of inactive thyroxine (T4) into active 3,5,3′-tri-iodothyronine (T3) [96]. Targeted disruption of TGR5 in mice showed significant fat accumulation with body weight gain compared with that of wild type mice when fed a high fat diet [98]. High expression of TGR5 in gall bladder was shown together with marked reduction in gallstone development in $TGR5^{-/-}$ mice on a lithogenic diet [99].

Estrogen is an important hormone in human physiology exerting its effect both at the transcriptional level as well as at the level of rapid intracellular signaling through second messengers [2–5]. Recent studies demonstrated that GPR30 responds to estrogen with rapid cellular signaling [2–5]. Prossnitz's review will be helpful to understand estrogen effects through plasma membrane GPCR [100].

2.4. Novel lipid mediators for pro- and anti-inflammatory process

Two novel structures of intercellular lipid mediators have been discovered as pro- and anti-inflammatory signals. Serhan's group discovered resolvin E1, a derivative from omega-3 fatty acid, as an anti-inflammatory and pro-resolving lipid mediator that plays important roles for the resolution of inflammation [101,102]. Claesson's group on the other hand elucidated that pro-inflammatory 14,15-leukotriene C_4, D_4 and E_4 were produced from arachidonic acid by 15-lipoxygenase in eosinophils and mast cells. They named them eoxins [103]. Both topics are reviewed in this special issue by Arita and Claesson, respectively [104,105].

Additionally, lipoaminoacids such as N-arachidonyl glycine and N-palmitoyl glycine are newly recognized lipid mediators especially in pain modulation and anti-inflammation [106–108]. This topic will be covered by Bradshaw [109].

3. Prospective remarks on intercellular lipid mediators and GPCRs

A change in our understanding of lipid molecules from structural components to signaling molecules might be the most impressive and surprising discovery of the last three decades. A description of lipid molecules in Lehninger's biochemistry textbook has changed from "structural and storage components without informational functions" in 1975 to "additionally some lipids serve as potent signals" in 2005 [110]. Development of analytical methods such as Mass spectrometry has contributed to the identification of novel lipid metabolites and will open new avenues in lipid biology.

In the future, we anticipate the discovery of many novel structures of lipid molecules and studies on their roles will focus on understanding lipid biology and developing new therapeutics based on the novel functions of these lipid molecules. Intercellular lipid mediators have been a platform for the development of new drugs such as prostaglandin analogues. Also, the discovery of the first sphingosine 1-phosphate receptor in 1998 was connected to