N-Palmitoyl Serinol

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Ceramides, a class of sphingolipids containing a backbone of sphingoid base, are the most important and effective structural component for the formation of the epidermal permeability barrier. While ceramides comprise approximately 50% of the epidermal lipid content by mass, the content is substantially decreased in certain inflammatory skin diseases, such as atopic dermatitis (AD), causing improper barrier function. It is widely accepted that the endocannabinoid system (ECS) can modulate a number of biological responses in the central nerve system, prior studies revealed that activation of endocannabinoid receptor CB1, a key component of ECS, triggers the generation of ceramides that mediate neuronal cell fate. N-palmitoyl Serinol is a kind of N-Acyl amide. It has the amide bond of AEA(Anandamide) and two hydroxy group of 2-AG(2-Arachidonoyl Glycerol), which is very similar structure with PEA(N-Palmitoyl ethanolamine).

ceramide epidermal barrier function endocannabinoid system endcannabinoid receptor skin inflammation AEA PEA 2-AG NEUROMIDE

1. Introduction

Human skin is composed of two major layers, the epidermis and, dermis, and each layer exhibits unique structural and physiological properties [1][2]. Because the outer layer epidermis is positioned at the interface with the environment, it mainly functions as a barrier to protect the body from harmful substances, such as UV irradiation, mechanical damage, and microorganisms [1][2]. A number of factors, e.g., structural and junctional proteins, lipids, and transcription factors, participate in the formation of the epidermal barrier [3]. While, in particular, cutaneous lipids serve as a key constituent to forming an optimal epidermal barrier, ceramides comprise approximately 50% of the intercellular lipid content by mass and signal to modulate multiple cellular functions, e.g., cellular proliferation, differentiation, and apoptosis. Alterations in the epidermal ceramide content have been characterized in certain inflammatory skin diseases, including atopic dermatitis (AD) [4]. In AD skin lesions, the content of ceramides containing long-chain fatty acids (FAs) (22–26 carbons in length) is significantly reduced, whereas ceramides with short-chain FAs (<20 carbons in length) are conversely elevated, leading to compromised barrier integrity [4].

It is widely accepted that the endocannabinoid system (ECS) is involved in multiple biological responses via the Gi/o protein-coupled receptor, known as endocannabinoid receptor CB1- and/or CB2-dependent mechanisms in different tissues, including skin, as follows [5]: (1) the activation of CB1 or CB2 increases endocannabinoid levels by inhibiting fatty acid amide hydrolase or adenylyl cyclase, which in turn activates intracellular kinases such as extracellular-signal-regulated kinase (ERK); (2) CB1/2 modulates certain ion channels, i.e., inhibition of N- and

P/Q-type voltage-sensitive calcium channels, and activation of potassium channels [6]. In addition to these established G-protein-coupled events, recent studies revealed that activation of CB1 is tightly associated with the generation of cellular ceramides [7][8]. In the skin, the ECS is profoundly involved in the regulation of epidermal homeostasis, e.g., keratinocyte (KC) proliferation and differentiation. Activation of CB1 stimulates DNA methylation through mitogen-activated protein kinase-dependent pathways, resulting in the suppression of keratinocyte differentiation [9][10]. In addition, CB1/2-coupled signaling mechanisms in the modulation of epidermal KC proliferation have been reported [9].

However, even though ceramides are a key component in the formation of the epidermal barrier and serve as signaling modulators to regulate cellular functions, the impact of CB1 on the production of epidermal ceramides has not been studied. Thus, we assessed whether CB1 activation could stimulate ceramide production in inflamed cellular conditions, in which ceramides are significantly diminished. Here, we show that an IL-4-mediated decrease in overall ceramide levels was significantly stimulated in human KC following N-Palmitoyl Serinol (PS : Dr. Raymond Laboratories, Inc. Englewood Cliffs Nj, USA, Trade name NEUROMIDE), an analog of the endocannabinoid N-Palmitoyl ethanolamine, through increased activities of ceramide synthetic enzymes. Furthermore, PS selectively increases ceramide levels with long-chain FAs (22–26 carbons in length). Finally, we demonstrate that the activation of CB1 accounts for the PS-mediated increase in the content of total ceramide, as well as ceramides containing long-chain FAs. These studies illuminate that endocannabinoid-mediated activation of CB1 modulates the epidermal ceramide profile, contributing to the improvement of the epidermal barrier function of inflammatory skin diseases in which ceramides are diminished, such as AD and aged skin.

2. Current Insights

The outermost layer of the epidermis, stratum corneum (SC), is composed of corneocytes, which are embedded in extracellular lipids, including ceramides. SC functions as an epidermal permeability barrier to defend our body against external threats, such as UV irradiation and pathogens [11]. Ceramides, a class of sphingolipids containing a backbone of a sphingoid base (or referred to as sphingosine) that is linked to a fatty acid (FA) via an amide bond, are the predominant lipid comprising approximately 50% of the SC lipid content by mass, and the most effective structural component for the formation of the epidermal permeability barrier [11]. Ceramides are produced in the skin through two major pathways [12]: (i) the de novo synthesis pathway that is initiated by serine palmitoyltransferase (SPT) and catalyzes the condensation of serine and palmitoyl-CoA to produce 3-ketosphiganine, which is further metabolized to sphinganine. Sphinganine is then amide-linked (N-acylated) by ceramide synthases (CerSs) to generate ceramides with different acyl chain lengths; and (ii) the sphingomyelinase (SMase)-dependent hydrolysis of sphingomyelin, a key component of the plasma membrane. In the present study, we show that N-palmitoyl serinol (PS) differently regulates ceramide generation in different cellular conditions, i.e., stressed/diseased condition vs. un-stressed (normal) condition. Because an IL-4-mediated decrease in ceramides could cause abnormal barrier functions—induction of excessive transepidermal water loss, and an increased risk of pathogenic infection—PS likely accelerates the enhancement of the skin barrier function by a prompt increase in ceramide content due to the SM hydrolysis pathway, through activation of SMases in the plasma membrane as well

as the SPT/CerS-mediated de novo synthesis pathway under stressed conditions, compared with un-stressed conditions, in which the SPT-mediated de novo synthesis pathway is only operated.

Prior studies have demonstrated that epidermal ceramide levels are altered (increased or decreased) in certain skin inflammatory environments, such as atopic dermatitis (AD) [13]. Ceramide levels are significantly reduced in the lesional skin of patients with AD, a chronic inflammatory skin disease in which the Th2 cytokines, e.g., IL-4 and IL-13, are key drivers involved with the underlying inflammatory process [14]. In particular, ceramides containing long-chain FAs (22–26 carbons in length) are significantly decreased, while ceramides with short-chain FAs (<20 carbons in length) are, conversely, increased in the lesional skin of patients with AD [15][16][17]. Of six CerS isoforms, both CerS2 and CerS3 are expressed at high levels in the skin and have been shown to synthesize the longer ceramide species; whereas other isoforms of CerS are associated with the production of ceramide species containing the shorter FAs [15][16]. Consistent with these findings, PS selectively activates CerS2 and CerS3 to elevate ceramides with 22–26 carbon-containing FAs, which are particularly responsible for the formation of the epidermal permeability barrier in both un-stressed or stressed conditions.

The endocannabinoid system (ECS) has lately been proven to be an important signaling network that modulates a wide range of biological responses in multiple tissues, including the skin, which expresses endocannabinoids such as anandamide, 2-AG, and the endocannabinoid receptor CB1 and/or CB2 [8][18]. Prior studies showed that endocannabinoids could regulate ceramide production via the endocannabinoid receptor CB1-mediated signaling events in certain neuronal cells or cancer cells, e.g., astrocytes, glial cell, glioma cell, as follows [5][8][19]: (i) CB1 activation increases the catalytic action of SMase, which hydrolyze SM to ceramide in the plasma membrane via the factor associated with neutral SMase (FAN)-containing signaling complex-mediated cellular mechanism; (ii) CB1 activation stimulates the activity of de novo synthetic SPT that increases condensation of serine and palmitoyl-CoA to produce ceramide. However, to our knowledge, it has not been identified if the endocannabinoid receptor CB1 is coupled to the generation of ceramide in the skin. We demonstrate here that PS, an analog of the endocannabinoid N-palmitoyl ethanolamine, increases ceramide production by both de novo synthesis and SM hydrolysis pathways to stimulate epidermal barrier integrity under an in vitro AD-like model. Although we first showed the relationship of ECS and ceramide generation in the skin, further studies are still needed to identify the more detailed mechanism(s) of how PS stimulates ceramide production, i.e., the involvement of the FAN-containing signaling complex.

In summary, the PS-mediated activation of CB1 accounts for the generation of epidermal ceramides through the de novo synthesis and SM hydrolysis pathways. In particular, PS selectively elevates ceramides with 22–26 carbon-containing FAs via activation of CerS2 and CerS3. These findings indicate that PS likely contributes to improving the epidermal barrier function of certain skin diseases, such as atopic dermatitis and aged skin, in which ceramide levels are dramatically diminished. Hence, pharmacological modulation of CB1 by endocannabinoids, or its analogs, might be considered as therapeutic and/or preventive strategies for such skin conditions.

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