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Allosteric Streams are Sensitised by Dihydroceramides Derived from Bacteroidetes Species

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Introduction

Bacterial colonisation of open wounds is common, and patients suffering from infected wounds frequently report significantly increased pain sensitivity at the wound site. Transient Receptor Potential Vanilloid Type 1 channels are known to be important in pain signalling and may become sensitised in pro-inflammatory conditions. Bacterial membrane components such as phosphoethanolamine dihydroceramide, phosphoglycerol dihydroceramide, and lipopolysaccharide are released into the environment by Gram-negative Bacteroidetes bacteria colonising infected wounds. We used intracellular calcium imaging and patch-clamp electrophysiology to see if bacterially derived PEDHC, PGDHC, or LPS can modulate the activity of TRPV1 channels expressed heterologously in HEK cells. PEDHC and PGDHC were found to sensitise TRPV1 in a concentration-dependent manner, whereas LPS treatment had no effect on TRPV1 activity in HEK cells.

TRPV1 channels are known to play an important role in pain signalling and are abundant on nociceptive nerve endings that innervate the skin and tooth pulp. TRPV1 channels are Ca2+ permeable and are activated by heat, acid, capsaicin, and a variety of endogenous mediators. Surprisingly, TRPV1 can be sensitised and exhibits an enhanced response to its agonists in the presence of prostaglandins, histamine, or H+.

Although clinical evidence suggests that peripheral TRPV1 nociceptive nerves are important for wound healing, TRPV1 sensitization may contribute to the hyperalgesia seen in patients with infected wounds. Indeed, patients with bacterially infected wounds experience more pain than those with uninfected wounds. Bacteroidetes, Gram-negative, and anaerobic bacteria have been found to colonise wounds. Bacteroidetes fragilis was found in infected postsurgical sites, and Bacteroidetes pyogenes was discovered in polymicrobial animal-bite wounds and diabetic foot infections. Lipopolysaccharides (LPS) are released into the environment by Bacteroidetes species, and LPS may be responsible for the hyperalgesia seen in patients with infected wounds, exacerbating pain by sensitising neuronal TRPV1 via the Toll-like receptor [1].

Description

LPS is not, however, the only bacterial component shed by Bacteroidetes species. A new class of sphingolipids has been discovered in gut and oral Bacteroides species. This new group includes phosphoethanolamine dihydroceramide and phosphoglycerol dihydroceramide, both of which are produced and shed in significant amounts by Bacteroides species. A growing body of evidence suggests that cell-permeable dihydroceramides may promote inflammation independently of TLR4-mediated canonical signalling. These bacterial-derived molecules may also have a stronger effect on the TRPV1 protein. We used intracellular calcium imaging and patch-clamp electrophysiology to see if PEDHC, PGDHC, or LPS can sensitise human TRPV1 channels to capsaicin activation in the HEK heterologous expression model lacking the TLR4 receptosome.

As a result, we used this heterologous mammalian expression model to determine whether the possible effects of the bacterial components on the human TRPV1 channel heterologously expressed in HEK cells are mediated by a CD14 or an MD2 independent pathway. PEDHC and PGDHC are structurally similar to mammalian dihydroceramides and sphingomyelin. Ceramide and sphingosine have previously been shown to have no effect on TRPV1 function in trigeminal neurons or TRPV1-expressing CHO cells [2].

TRPV1 activity was inhibited in trigeminal neurons and TRPV1-CHO cells when lipid rafts containing sphingomyelin were disrupted by depleting cholesterol or cleaving sphingomyelin with sphingomyelinase, indicating the importance of lipid rafts for TRPV1 function. These findings also suggested that sphingomyelin could play a role in TRPV1 activation. Thus, our findings support the role of a sphingomyelin-like molecule in TRPV1 activity. It was discovered that the vanilloid binding site of the TRPV1 protein contains a resident phosphatidylinositol lipid, and that vanilloid agonists, such as capsaicin, must displace the endogenous lipid to activate the channel. The TRPV1 protein also has C-terminal binding sites for phosphoinositide 4,5-bisphosphate. PEDHC's molecular structure is similar to that of phosphatidylinositol lipids.

PEDHC could thus bind to the TRPV1 protein within or near the capsaicin binding site or its C-terminus. Phosphoinositides, on the other hand, have been proposed to modulate TRPV1 function indirectly via a membrane protein called Pirt. It is currently unknown whether PEDHC or PGDHC directly interact with the TRPV1 protein or whether the effects of these dihydroceramides are due to an indirect action via other proteins or intracellular signalling pathways that contribute to TRPV1 function modulation. We discovered that LPS-PG pretreatment had no significant effect [3-5].

Conclusion

In conclusion, our findings suggest that PEDHC and PGDHC may both contribute to TRPV1 channel sensitization in a concentration-dependent manner, whereas LPS-PG did not cause significant TRPV1 sensitization. TRPV1 was not activated by PEDHC or PGDHC alone. Because PEDHC was effective at a higher concentration of 10 g/mL in our fluorescence imaging experiments, it appears to be a less potent TRPV1 sensitizer than PGDHC. In our fluorescence imaging experiments, PGDHC efficiently sensitised TRPV1 at a lower concentration of 1 g/mL. PEDHC may have had a lower affinity for its cellular target in TRPV1-HEK cells. However, more research is needed to confirm or refute this hypothesis. More in vivo research is required to determine whether any of the shed bacterial products affect pain sensitivity.

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Conflict of Interest

There are no conflicts of interest by author.

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