Human eosinophils and neutrophils biosynthesize novel 15-lipoxygenase metabolites from 1-linoleoyl-glycerol and N-linoleoyl-ethanolamine

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BACKGROUND

The endocannabinoids 2-AG and AEA are lipids regulating many physiological processes, notably inflammation. The endocannabinoidome includes other monoacylglycerols (MAG) and N-acyl-ethanolamines (NAE) such as 1-linoleoyl-glycerol (1-LG) and N-linoleoyl-ethanolamine (LEA). Endocannabinoid hydrolysis inhibitors are now being tested as potential anti-inflammatory agents. By increasing MAG and/or NAE levels, these inhibitors will likely increase the levels of their metabolites. Herein we investigated whether 1-LG and LEA were substrates for the 15-lipoxygenase pathway, which is strongly involved in asthma and its severity. We thus assessed how human eosinophils and neutrophils biosynthesized the 15-lipoxygenase metabolites of 1-LG and LEA. Linoleic acid (LA), a well-documented substrate of 15-lipoxygenases, was used as positive control.

RESULTS

We synthesized the putative 15-lipoxygenase metabolites of 1-LG and LEA using Novozym435 and soybean lipoxygenase. Eosinophils, which express the 15-lipoxygenase-1, metabolized LA, 1-LG, and LEA into their 13-hydroxy derivatives. This was almost complete after 5 minutes. Substrate preference of eosinophils was LA>LEA>1-LG. Human neutrophils, which express the 15-lipoxygenase-2, also metabolized LA, 1-LG, and LEA into their 13-hydroxy derivatives. This was maximal after 30 seconds. Substrate preference was LA≫1-LG>LEA. Importantly, the new 15-lipoxygenase metabolites we disclose were found in tissues from humans and mice.

CONCLUSIONS

We successfully showed that human eosinophils and neutrophils transforms 1-LG and LEA into novel 15-lipoxygenase metabolites. How these new metabolites modulate the inflammatory cascade is now being explored.