Nuclear Receptor Activation by ω3-Polyunsaturated Fatty Acids

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Introduction

Two essential polyunsaturated fatty acids (PUFAs) are linoleic acid (LA), which is an omega-6 (ω-6) fatty acid, and α-linolenic acid (ALA), which is an n-3 fatty acid. In some situations, such as LA and/or ALA deficiencies, arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be considered conditionally essential. Although many fats have been associated with increasing the risk of cardiovascular disease (CVD) such as saturated and *trans* fatty acids, EPA and DHA have a variety of beneficial health effects. The question is why some PUFAs, in particular the ω-3 PUFAs (ALA, EPA, and DHA), are associated with reduced risk of CVD whereas closely related ω-6 PUFAs (LA, AA) are, either not as effective or are detrimental to heart health? One explanation may be inhibition of ω-6 metabolism by these other structurally similar compounds. Another explanation, and the option explored here, is that receptors exist that preferentially respond to a particular structure of fatty acid. These specific "lipid sensors" would affect gene expression in a tissue-specific, gender-specific, and developmentally specific manner and thereby affect the development of CVD.

Methods

All nuclear receptor assays were performed using the kits available from **INDIGO Biosciences, Inc.** (State College, PA), using the manufacturer's instructions, The fatty acids were purchased from Enzo Life Sciences (Farmingdale, NY) and conjugated to bovine serum albumin (BSA).

Results

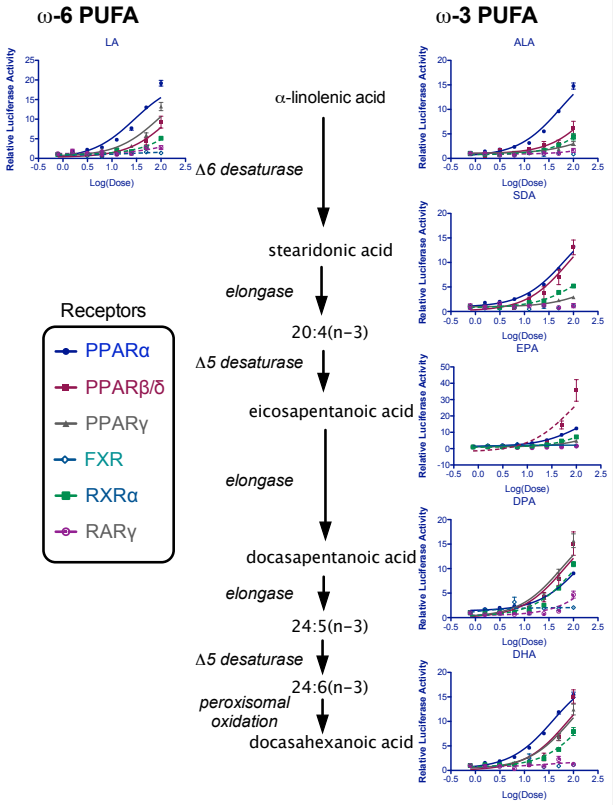

Figure 1 . Examination of activation of nuclear receptors by ω3 and ω6 PUFAs. Shown are the nuclear receptors whose activity was significantly affected by at least one fatty acids. Peroxisome proliferator-activated receptor (PPAR), α β/δ and γ; Retinoid X receptor (RXR) α; farnesoid X receptor (FXR); and Retinoic Acid Receptor (RAR) γ. (Inactive receptors are shown in Figure 3.)

Results

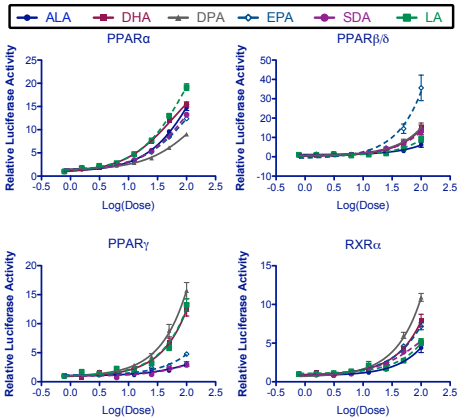

Figure 2 . Nuclear receptors that are responsive to ω3 and ω6 PUFAs. Dose-response with each fatty acid, 1.5 to 100 µM (n=6, mean ± SEM).

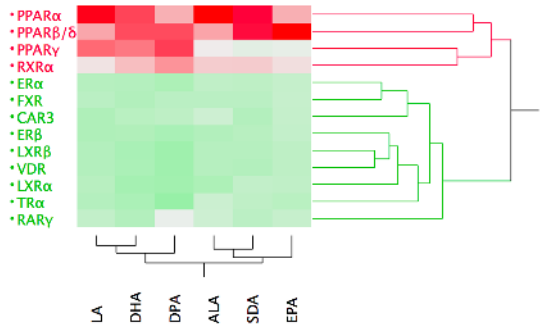

Figure 3 . A subset of nuclear receptors are responsive to ω3 and ω6 PUFAs. Hierarchical clustering of all nuclear receptors tested, data shown for the 100 µM dose. Red represents an increase in activity, green is basal or decreased activity with white as intermediate.

Conclusions

Several nuclear receptors are activated by dietary fatty acids, including PPARα, β/δ, γ, RXRα and RARγ. Whereas PPARα and β/δ are regulated by all fatty acids, some of the other receptors are more discriminating, such as PPARγ and RXRα. More research is required to determine if this specificity is the reason for CVD protection.

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