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Docosapentaenoic acid derived metabolites and mediators – The new world of lipid mediator medicine in a nutshell

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ABSTRACT

Recent years have seen the description and elucidation of a new class of anti-inflammatory and pro-resolving lipid mediators. The arachidonic acid (AA)-derived compounds in this class are called lipoxins and have been described in great detail since their discovery thirty years ago. The new players are mediators derived from fish oil omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), called resolvins, protectins and maresins. Taken together, these mediators are also called specialized pro-resolution mediators (SPMs). As compared to the AA/EPA/DHA-derived compounds, research regarding mediators formed from the n-3 and n-6 docosapentaenoic acids (DPAn-3 and DPAn-6) is sparse. However, mono- di- and trihydroxy derivates of the DPAs have anti-inflammatory properties as well, even though mechanisms of their anti-inflammatory action have not been fully elucidated. This review aims to summarize current knowledge regarding the DPA-derived SPMs and their actions.

1. Introduction

Arachidonic acid (AA), a 20-carbon (C20) polyunsaturated fatty acid (PUFA) with a double bond in the omega-6 position is firmly established as a precursor of potent lipid hormones such as prostaglandins and leukotrienes (Samuelsson, 1979). Long-chain omega-3 PUFAs, differing in the position of their first double bond from the methyl terminus, have been described as biologically acive compounds since the 1970s. But only recent years have seen the elucidation of a large variety of highly bioactive lipid hormones derived from the two most prominent of these fatty acids, the C20 eicosapentaenoic acid (EPA) and the C22 docosahexaenoic acid (DHA) (Hong et al., 2003; Serhan et al., 2000, 2002). Together with the lipoxins (derived from the omega-6 fatty acid AA), omega-3 PUFA-derived lipid mediators of the resolvin, protectin and maresin families form a large group of anti-inflammatory compounds that have been implicated in the active resolution of inflammation: They are thus called specialized pro-resolving mediators (SPMs). These compounds were found to have functions in inflammation protection as well as in pain alleviation, host defense and organ protection from ischemia-reperfusion damage (Serhan, 2014). Several mechanisms have been shown to lead to these actions that are specific for a given SPM: RvE1 inhibits NF-kB activation (Arita et al., 2005), RvD1 and PD1 modulate macrophage activity by e.g. miRNA (Li et al., 2013), and many SPM increase phagocytosis (Chiang et al., 2015; Colas et al., 2014; Serhan, 2014). Instrumental in the formation of the omega-3 derived resolvin/protectin precursors 18R/S-HEPE and 17R/S-HDHA and the subsequent di- and trihydroxy resolvins/protectins themselves are lipoyxgenases such as ALOX15 and ALOX5 (Dobson et al., 2013; Weylandt et al., 2012), as well as the acetylated cyclooxygenase 2 (COX-2) formed by treatment with aspirin (Sun et al., 2007). Recent studies have confirmed presence of DHA-derived SPMs in human plasma and serum as well as increased formation in the context of increased omega-3 PUFA or aspirin intake (Colas et al.,

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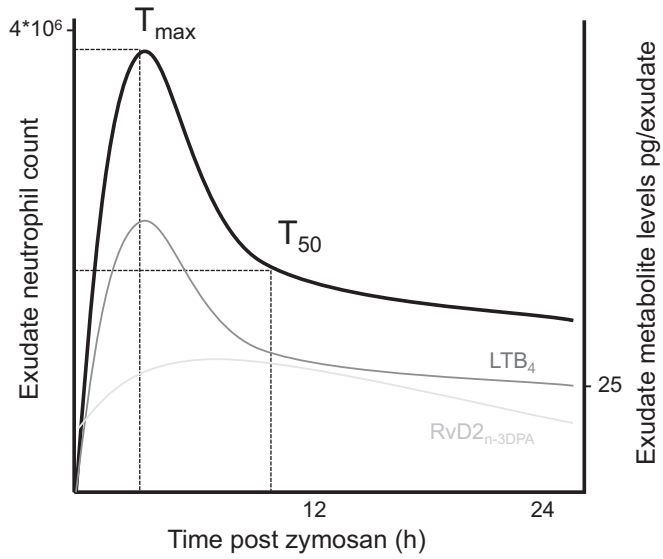

Fig. 1. An established tool in the assessment of acute inflammation resolution in vitro is the neutrophil count in peritoneal exsudates in zymosan peritonitis (Serhan et al., 2008), as schematically illustrated here: Resolution of inflammation can be quantified by the time point (T_{max}) when neutrophil numbers reach maximum, the duration (T_{50}) when the neutrophil numbers are reduced to 50% of the count at T_{max}, defining the resolution interval (R_i) as the time interval between the maximum neutrophil count (T_{max}) to the 50% reduced count (T_{50}). SRMs can be described in the temporal dynamics of their formation within this process: The concentration of the pro-inflammatory leukotriene B4 esssentially follows the neutrophil curve (dark gray), while e.g. the curve for $RvD2_{DPAn-3}$ increases during resolution as schematically depicted as light gray line (modified from (Dalli et al., 2013)).

2014) and in urine (Sasaki et al., 2015a), human placenta (Jones et al., 2013) and human milk (Weiss et al., 2013).

A central concept in the approach to investigate SPMs is the analysis of self-limited (self-resolving) inflammatory exudates from zymosan-induced peritonitis in mice (Fig. 1). In these exudates hydroxy products derived from AA, EPA and DHA were discovered and characterized, thus establishing an entirely new field of inflammation resolution research (Serhan et al., 2015).

Beyond AA, EPA and DHA there are additional long-chain PUFAs, namely the omega-3 and the omega-6 C22 docosapentaenoic acids. These fatty acids also occur in diets particularly with high fish content or in algal products. Their biological role has not been subject to extensive studies as compared to AA, EPA and DHA (Fig. 2). However, given that these two PUFA are identical save for the difference in the (omega-3 versus omega-6) position of their double bonds, studying these fatty acids might actually enable the thorough elucidation of the importance of the omega-3 versus the omega-6 position of the last double bond for biological actions of these fatty acids.

2. The docosapentaenoic acids

Docosapentaenoic acid (DPA), a 22:5 long-chain PUFA, consists of two isomers: all-cis-7, 10, 13, 16, 19-docosapentaenoic acid (DPA, 22:5n-3) and all-cis-4, 7, 10, 13, 16-docosapentaenoic acid (DPA, 22:5n-6), and both isomers are abundant in fish oils due to their primary synthesis in algae and presence algal oils (Purwaha et al., 2011). DPA can also be generated by EPA and AA metabolism. EPA and AA are further converted to docosapentaenoic acid (DPA; 22:5n-3) and docosatetraenoic acid (DTA; 22:4n-6) by elongation of very long chain fatty acids protein 5 (ELOVL5) or an ELOVL2-like fatty acid elongase, and DTA can then be desaturated by Δ6-desaturase to give DPA (22:5n-6) and DHA (Dalli et al., 2013; Pauter et al., 2014).

The omega-6 docosapentaenoic acid, DPAn-6, has most extensively been described in context and in combination with the omega-3 DHA, as both are present in algal oils.

For example, anti-inflammatory effects have been described for DPAn-6 in vitro and in vivo, and neuroprotective effects have been described in combination with DHA (Green et al., 2007).

The omega-3 docosapentaenoic acid, DPAn-3 has been characterized as an inhibitor of platelet aggregation (Akiba et al., 2000; Murphy et al., 1997, 1999) and angiogenesis where it acts as a suppressor of expression of the vascular endothelial-cell growth factor receptor 2 (Tsuji et al., 2003). Furthermore, recent data indicate an anti-inflammatory effect of DPAn-3 in models of pulmonary hypertension (Morin et al., 2014) and arthritis (Morin et al., 2015), and antiproliferative effects in colon cancer cells (Morin et al., 2013). Similar to EPA and DHA, DPAn-3 – as well as DPAn-6-was found to improve lipoprotein profiles in hamsters on a high cholesterol diet (Chen et al., 2012). Indeed, another study found a DPAn-3 induced downregulation of genes involved in fat synthesis in liver cells (Kaur et al., 2011). A small human study administering a total of 8 g of a pure DPAn-3 supplement over 7 days demonstrated a significant increase of DPAn-3 content in plasma triglycerides and plasma phospholipids, but not in plasma chloesterol esters or red blood cells (Miller et al., 2013). As compared to this, a bioavailability study of DPAn-3 in rats fed a diet high in DPAn-3 (250 mg/animal/day) for 3 days showed a significant increase in DPAn-3 tissue levels in liver and heart, but no significant increase in plasma DPAn-3 levels due to supplementation (Ghasemi Fard et al., 2014).

Given the characterization of a multitude of hydroxy lipid

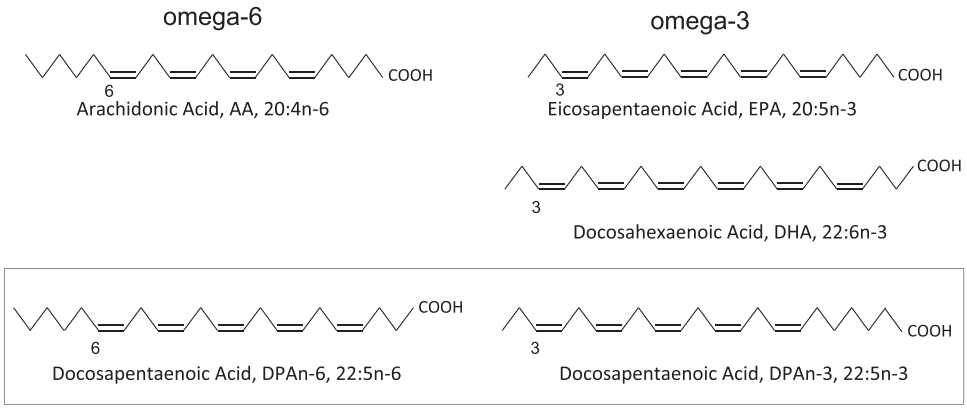

Fig. 2. Omega-6 and omega-3 polyunsaturated fatty acids serving as precursors for biologically active lipid metabolites and mediators. The only difference between the two docosapentaenoic acids is the position of their first double-bond.