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Bioactive lipids as new class of microglial modulators: When nutrition meets neuroimunology

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ABSTRACT

Within the central nervous system the traditional role of microglia has been in brain infection and disease, phagocytosing debris and secreting factors to modify disease progression. More recently, microglia have been found to be important for normal brain development, circuit refinement, and synaptic plasticity in ways that were previously unsuspected. Hence, the brain innate immune system appears to be key in all situations, ranging from physiology to pathology. This unique feature of microglia is established by the wide array of receptors it is equipped with to sense molecular patterns. This includes receptors to most if not all neurotransmitters, neuromodulators and purines. We here review novel, yet extensive literature on a new class of microglia modulators, namely bioactive fatty acids. These lipids are issued from metabolism of nutrients and can cross the blood brain barrier to reach the CNS. They appear to be direct modulators of microglial activity, triggering/inhibiting inflammatory processes or enhancing/inhibiting the ability of these cells to respond to hazardous agents.

Microglia is the main cellular component of the brain innate immune system and a key player in regulation and protection of the CNS homeostasis (Hanisch and Kettenmann, 2007). Over the last decade, it has become evident that microglia is multitasking and highly plastic cell, important for development and homeostasis of the CNS but also for deterioration of or recovery from pathological conditions though inflammatory as well as non-inflammatory responses (Ransohoff and Brown, 2012). Microglia, which is yolk sac derived and populates the brain early in embryogenesis, is also critical player in maintaining the functional and architectural homeostasis of the brain and its neurocircuitry (Wake et al., 2013). As such, it plays key roles in the remodeling of neurological circuits (Schafer et al., 2012), in synaptic pruning (Paolicelli et al., 2011), and in neurogenesis (Sierra et al., 2010; Gemma and Bachstetter, 2013). Since recently, microglia cells are also known to sense and survey the microenvironment in the normal adult brain with their highly ramified and motile processes in order to detect any non-homeostatic stimulus and to influence neuronal structure and function (Davalos et al., 2005; Nimmerjahn et al., 2005; Sipe et al., 2016; Tremblay et al., 2010; Wake et al., 2009). The multifunctional roles of microglia are part of environmental monitoring that is designed to sense perturbations and to orchestrate the specific repertoire of microglial functions to maintain homeostasis.

Under pathological conditions, microglia responds to alterations of the CNS by activation and potential redirection of its phagocytic activity from synaptic pruning to the clearance of hazardous factors (Ransohoff and Perry, 2009; Sierra et al., 2014; Tay et al., 2016). Modification in the concentration of some factors or appearance of unusual molecules in the extracellular milieu is likely to be the trigger for microglial activation (Block et al., 2007; Kettenmann et al., 2011; Sierra et al., 2014). As such, microglia is believed to prominently contribute to CNS pathologies, including their establishment, perpetuation, and resolution. Yet, long-lasting chronic inflammation is proposed to drive the physiological functions of microglia off balance (Ransohoff and Perry, 2009).

The uniqueness of microglia is established by the wide array of receptors it is equipped with to sense molecular patterns. This includes receptors to most if not all neurotransmitters, neuromodulators and purines (for review, Pocock and Kettenmann, 2007), receptors to immune signals such as Toll-Like Receptors (Kreutzberg, 1996), receptors which enable microglia to recognize its targets to phagocyte (the so-called "eat-me" signals) and discriminate them from the remaining parenchyma, particularly from living cells (which express "don't-eat-me" signals) (Brown and Neher, 2014). The variety of signals that control microglia can be subdivided into two categories: 'Off' signals which constitutively keep microglia in its homeostatic state; 'On' signals which are inducible and activate microglia.

The remarkable and complex receptology of microglia led to the concept of "microglial sensome", a sensing apparatus that is unique to this cell (Hickman et al., 2013). Two groups described the distinct transcriptomic signature of microglia including expression of a unique

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cluster of transcripts encoding proteins for sensing endogenous ligands and microbes (Hickman et al., 2013; Butovsky et al., 2014). These molecular toolsets enable microglia to respond to many extraneous cues and to adapt its activity to environmental variations.

Recent studies indicate that a number of naturally occurring bioactive compounds present in certain foods, such as fatty acids, target microglia (Bazinet and Laye, 2014; Johnson, 2015; Vauzour et al., 2015). Indeed, bioactive fatty acids issued from nutrition can cross the blood brain barrier and reach the CNS. These lipids are not energy suppliers for the brain, yet they can accumulate locally and be sensed by the cells (Bazinet and Laye, 2014; Rasmussen et al., 2012) (Fig. 1). We now benefit from extensive demonstration that fatty acids (such as saturated fatty acids or polyunsaturated fatty acids) are direct modulators of microglial activity, triggering/inhibiting inflammatory processes or enhancing/reducing the ability of these cells to respond to hazardous agents. Moreover, while the link between bioactive fatty acids and microglia receptology has not been clarified yet, microglia expresses a wide range of lipid metabolism-related genes as well as lipid-sensitive receptors such as Toll-Like Receptors (TLRs), CD36, receptors for endocannabinoids, prostaglandins, phospholipids, etc. (Brown and Neher, 2014; Kettenmann et al., 2011; Mauerer et al., 2009; Mecha et al., 2015).

1. Modulation of microglial activity by saturated fatty acids (SFAs)

Several studies demonstrate that an excess intake of dietary fat translates into increased lipid content in the hypothalamus, a brain area that exerts central control over glucose, fat, and energy metabolism (Morselli et al., 2014; Martinez de Morentin et al., 2010). The build-up of dietary lipids in the brain (Morselli et al., 2014; Martinez de Morentin et al., 2010), particularly SFAs species, is paralleled by hypothalamic inflammation (Valdearcos et al., 2014; Argente-Arizon et al., 2015). Recent studies established SFAs entry into the CNS as the potential nutritional trigger of hypothalamic inflammation in the context of DIO, which could play a critical role in the development of obesity-related diseases such as metabolic syndrome (Posey et al., 2009; Valdearcos et al., 2014) (Fig. 2).

In 2014, Valdearcos et al. showed that microglia is highly sensitive to DIO-induced SFAs accumulation into the hypothalamus (specifically palmitic acid that increase by ~40% over chow diet), and responds to this extraneous cue by mounting an inflammatory response in the hypothalamus (Thaler et al., 2012; Valdearcos et al., 2014; Gao et al., 2014). This effect can be mimicked by gavage with SFA-rich diet. More evidence came from in vitro experiments. When treated for 24 h with SFAs of varying chain lengths (C12:0, C14:0, C16:0, C18:0), microglia in primary culture mounts an inflammatory response, releasing Interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF-α) and Monocyte Chemotactic Protein-1 (MCP-1). Long-chain SFAs such as palmitic acid (C16:0) are generally more potent activators of microglia than shorter chain SFAs. Conversely, fatty acids of other saturation status (C16:1, C18:1-olive oil, C18:2) do not activate inflammatory factors release or activation of the inflammation-related signaling pathway NFκB (Valdearcos et al., 2014). This confirmed studies performed on the BV2 microglial cell line demonstrating that palmitate (C16:0) induces the release of pro-inflammatory factors when applied for 4 h (Duffy et al., 2015) or 24 h (Button et al., 2014) on cultures. One study however could not observe any inflammatory action of palmitic acid when applied on BV2 cells (Tracy et al., 2013). They showed that incubation with the fatty acid changed the reactivity of microglia to an inflammatory challenge, significantly enhancing the production of cytokines

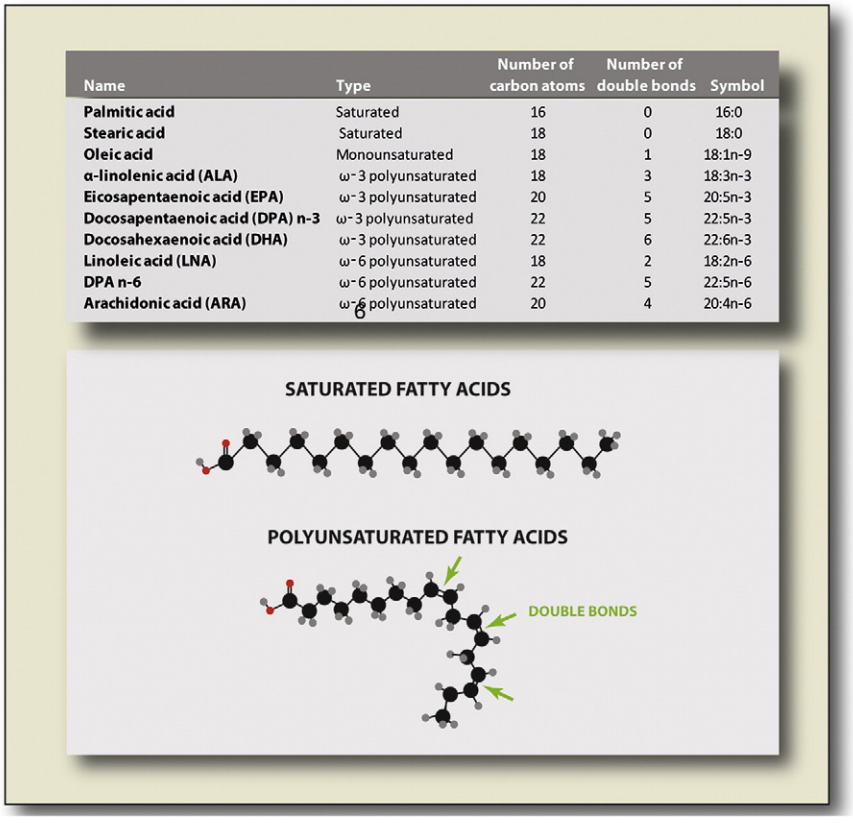

Fig. 1. Fatty acid classification. Fatty acids are classified by their carbon chain length and by their number of double bonds. Within the brain, palmitic acid and stearic acid are the main saturated fatty acids, and oleic acid is the main monounsaturated fatty acid. The polyunsaturated fatty acids (PUFAs), which contain multiple double bonds between carbon atoms, can be classified into two families depending on the position of the double bond on the methyl terminal (ω; n-) end. The two predominant PUFAs in the brain are n-6 arachidonic acid (AA) and n-3 docosahexaenoic acid (DHA). In the brain, fatty acids are predominantly esterified to phospholipids in the plasma membrane. Phospholipids containing DHA are enriched in grey matter and the synaptosomal fraction, whereas other esterified fatty acids, such as palmitate and oleate, are enriched in myelin.