Nutrition 30 (2014) 1104–1109

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Polyunsaturated fatty acids and gliomas: A critical review of experimental, clinical, and epidemiologic data

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ARTICLE INFO

Article history:
Received 11 January 2014
Accepted 12 January 2014

Keywords:
Polyunsaturated fatty acids
Essential fatty acids
Glioma treatment
Central nervous system tumors

ABSTRACT

Certain polyunsaturated fatty acids (PUFAs) called essential fatty acids (EFAs) cannot be biosynthesized by the body and hence, need to be obtained from diet. These PUFAs and their metabolites have multiple physiological functions that are altered in tumor cells due to a decreased expression of Δdelta-6-desaturase, which is an essential step in their metabolism. As a result, tumor cells would be protected from the toxic effect caused by free radicals, one product of EFA metabolism. EFAs have been proposed to have therapeutic potential in the treatment of glioblastoma. Gliomas are the most common primary tumors of the central nervous system in children and adults. High-grade gliomas remain a therapeutic challenge in neuro-oncology because there is no treatment that achieves a significant improvement in survival. Novel therapeutic strategies that use PUFAs for the treatment of gliomas have been assessed in cell cultures, rodent glioma models, and humans, with encouraging results. Here we review the latest progress made in the field.

Essential polyunsaturated fatty acids: Metabolism and function

Lipids are a heterogeneous group of substances widely distributed in animals and plants that play important roles in human biology. Polyunsaturated fatty acids (PUFAs) that contain ≥2 double bonds, and cannot be biosynthesized by the human body are called essential fatty acids (EFAs), and their dietary intake is essential for homeostasis [1]. The terms *PUFAs* and *EFAs* are here used synonymously, although this is not strictly correct.

EFAs include the "ω-3" series derived from α-linolenic acid (ALA, 18:3, ω-3) and the "ω-6" series derived from *cis*-linolenic acid (LA, 18:2, ω-6) [2,3].

Once they are acquired by dietary intake, both LA and ALA are transformed by cellular enzymes, such as desaturases and elongases, into intermediate and final metabolites, which play different physiological roles (Fig. 1). EFAs and their metabolites have been shown to affect tumor cell survival in vitro and in vivo in a wide range of tumors [2,4].

In many tumor cells, EFA metabolism is abnormal because there is a decrease in delta-6-desaturase (D6D) enzymatic activity, which is an essential step for γ-linolenic acid (GLA) formation. However, metabolites derived from the ω-3 series are not affected because they can be obtained from diet [5]. GLA, arachidonic acid (AA), and eicosapentaenoic acid (EPA) possess tumoricidal action due to their ability to produce free radicals that lead to lipid peroxidation [6–8]. Thus, it is believed that a decrease in D6D activity would constitute a protective mechanism used by cancer cells to avoid the cytotoxic effects of EFAs.

It has been suggested that EFAs have therapeutic potential in the treatment of glioblastoma (GB). Factors involved in glioma genesis are multiple and include not only genetic predisposition but also environmental exposure [9]. Dietary nutrients and anti-inflammatory agents that may be involved in glioma risk and

This work was supported by funds provided by CONICET and SECYT-UNC (Argentina). SSS designed and performed revision and wrote the paper. GR designed, wrote, and corrected the manuscript. EAR designed and directed the work and corrected the manuscript. CM designed and corrected the manuscript. The authors declare that they have no competing interests.
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http://dx.doi.org/10.1016/j.nut.2014.01.009

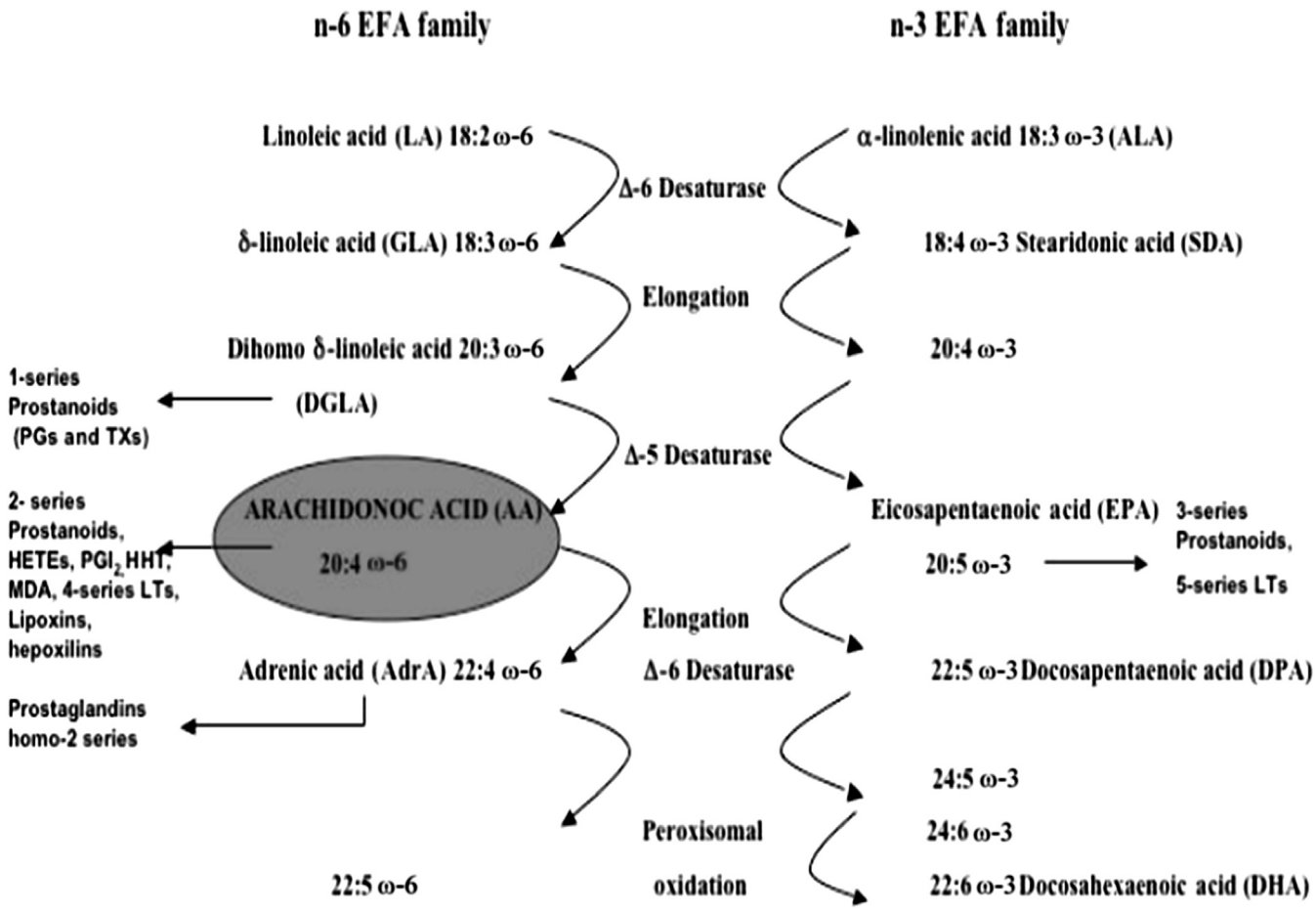

Fig. 1. Cellular pathways of metabolism of ω-3 and ω-6 of polyunsaturated fatty acids. Adapted from Pasqualini ME, Berra MA, Yurawecz MP, Repossi G, Eynard AR. Dietary manipulation of precursor polyunsaturated fatty acids modulates eicosanoid and endocannabinoid synthesis: A potential tool to control tumor development. *Curr Nutr Food Sci* 2008;4:161–75.

progression have been studied. It has been reported that the composition of EFAs differs between glioma tissue and non-neoplastic brain and that these fatty acids exhibit tumoricidal activities without significant side effects. Hence, it has been questioned whether GLA administration may be a suitable adjuvant therapy for the treatment of gliomas or the prevention of recurrences [10].

Gliomas: General features

Gliomas are central nervous system (CNS) tumors of glial origin [10]. The term *glioma* includes the following neoplasms:

1. ependymal tumors, which resemble ependymal cells;
2. astrocytic tumors, which resemble astrocytic cells; and
3. oligodendroglial tumors, which resemble oligodendroglia.

Classification

These tumors are classified according to the 2007 World Health Organization grades, which are a modification of the St. Anne-Mayo grading system scheme [11]. According to this system, tumors with low proliferative potential and with possibility of cure following surgical resection alone are grade I. Grade II lesions are generally infiltrative in nature and often recur. Grade III includes tumors with histologic evidence of malignancy, including nuclear atypia and high mitotic activity. Grade IV is assigned to tumors looking cytologically malignant, mitotically active, with necrosis often associated with bad evolution and fatal outcome [12]. Furthermore, it is considered that GBs (grade IV astrocytomas) can come from two progression pathways, which correlate with two different entities based on their molecular profile. Primary GBs are characterized by a relatively high frequency of epidermal growth factor receptor gene amplification, phosphatase and tensin homolog gene deletion, and cyclin-dependent kinase inhibitor 2 A (p16) loss. Secondary GBs or type 1 GBs, progress from lower grade astrocytic tumors that contain *TP53* mutations [13].

Epidemiologic features

A large epidemiologic study of glial and non-glial brain tumors (N = 45,000) in Europe reported that 86% were astroglial, 6.4% oligodendroglial, and 3.6% ependymal [14].

A recent study estimating the prevalence of primary brain tumors in the United States reported that the overall incidence rate for primary brain tumors was 18.1 per 100 000 person-years. The glioma subgroup was comprised mainly of malignant tumors (96.4%), GBs representing 53.5% of them [15].