Journal of
Bioresearch Communications

Siddiqui et al., J Biomol Res Ther 2013, 2:3
DOI: 10.4172/2167-7956.1000e119

Editorial Open Access

Docosahexaenoic Acid: A Potential Modulator of Brain Tumors and Metastasis

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Although not specific to any particular region in the brain, primary tumors and/or metastases from other organs are life threatening and mortality is rapid. Treatment options for patients with primary brain tumors or metastases are limited and include (either alone or combined) whole-brain radiotherapy, cranial stereotactic radiosurgery, neurosurgery, and steroids [1,2]. However, the standard treatment for multiple brain lesions remains whole-brain radiation (WBRT) for symptom control. For cancer patients treated with WBRT, median survival is 3–6 months; in patients treated with steroids alone, 6–8 weeks; and for untreated patients with symptomatic brain metastasis, median survival is less than one month [3,4]. Furthermore, these treatments do not improve the quality of life and adversely affect cognitive functions. Clearly, patients who have brain tumors or are at risk of developing metastatic tumors need other treatment options.

The human brain contains nearly 60% fat, mostly in the cellular membranes. The lipid composition of the cellular membrane varies among cells of different organs and tissues. The lipid composition within cells also varies among plasma membranes, endoplasmic reticulum, mitochondrial membranes, and nuclear membranes. The biophysical properties of a membrane are regulated by the relative amounts and types of fatty acids present within the membrane's phospholipid bilayer. Since the membranes are home to nearly 1/3 of all cellular proteins, including enzymes, transport proteins, ion channels, receptors, adhesion proteins, and components of cellular signaling pathways, the composition of these cellular membranes is extremely critical for cell responsiveness under normal and pathological situations. In the brain, neuronal membranes contain phospholipids that are predominantly rich in docosahexaenoic acid (DHA), the most unsaturated of the long-chain omega-3 fatty acids [5-7]. DHA, particularly abundant in cold-water fatty fish, has been excellently reviewed in recent articles for its role in brain development and intelligence [8-12]. Some authors have suggested that early humans who lived near water sources and ate seafood experienced a significant change in their brains, acquiring learning capabilities and intelligence that has revolutionized life on planet earth [13,14]. In contrast, Australopithecines did not have access to omega-3 fatty acids and, for 3 million years, got stuck at a brain capacity that was not much bigger than a chimpanzee's.

The importance of DHA in learning, intelligence, Alzheimer disease, stroke, and traumatic brain injury has been highlighted in several excellent, recent studies [15-23]; however, its role in primary brain tumor development and metastasis from the cancers of other organs has not been so apparent. The importance of DHA in brain function was only realized in the late 1980s and early 1990s; Stein et al. as early as 1963, developed an interest in the fatty acid composition of brain tumors [24] and subsequently reported that transmissible glial tumors implanted in mice intracerebrally or subcutaneously contained 70-80% less DHA than normal brain tissues [25]. This work demonstrated that tumors have specific lipid pattern, which is independent of tumor location. Similarly Martin et al. in 1996 reported that human gliomas contained almost 50% less DHA in both total lipid or phospholipid fractions than normal brain tissues [26]. Another study also found significantly low levels of total omega-3 fatty acids and DHA in 19 patients with gliomas and meningiomas compared to control human brain tissues [27]. The DHA in phospholipids was also found to be significantly reduced (by 60-70%) in human neuroblastoma cells compared to human and rat cerebellum tissue [28]. We have also found low DHA levels in gliomas (unpublished data) in comparable ranges as reported by Martin et al. [26]. Furthermore, a study published in 2003 on childhood cancer among Alaska Natives, who primarily eat food from marine sources rich in omega-3 fatty acids and DHA, reported almost 10 times less incidences of neuroblastomas compared to the US white population [29]. These observations imply that a deficiency of omega-3 fatty acids, particularly DHA, may be linked to the development of brain tumors. Consistent with these findings, prophylactic treatment with DHA delayed neuroblastoma development and inhibited the growth of established tumors in a mouse xenograft model [30]. These observations clearly suggest a profound role of DHA in regulating brain structure and metabolism that may offer a protection against developing primary brain tumors or metastasis from other cancerous sites to the brain. Furthermore, it is interesting to note that brain tumors are not only deficient in DHA content, but they also have elevated levels of proinflammatory AA [25,26, 28]. DHA and AA have antagonistic effects. For example, metabolites of AA, such as PGE2 and epoxyeicosanoids, stimulate brain tumor growth [31], whereas the metabolites of DHA, such as hydroperoxy fatty acids,neuroprotectin and resolvins, are protective [32-34]. A deficiency of DHA in brain tumors suggests that a predominance of AA metabolism creates more permissive conditions for tumor survival and growth.

Although controversial, Paget [35] introduced the "seed and soil" theory that tumor cells (seeds) could have a specific affinity for the microenvironment of certain organs (soil). Recent studies have supported this theory, showing that cancer metastasis depends not only on the ability of cancer cells to survive, proliferate, and promote vascularization, but also on the ability of the microenvironment surrounding the metastasis to regulate the area's metastatic potential. The brain is relatively protected from metastasis because its microvascular endothelial cells provide an active permeability barrier and transport system known as the blood-brain barrier (BBB). The BBB involves

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Received October 14, 2013; **Accepted** October 15, 2013; **Published** October 20, 2013

Citation: Siddiqui RA, Harvey K, Bammerlin E, Ikhlaque N (2013) Docosahexaenoic Acid: A Potential Modulator of Brain Tumors and Metastasis. J Biomol Res Ther 2: e119. doi: 10.4172/2167-7956.1000e119

the participation of astrocytes, pericytes, and endothelial cells and has characteristically complex tight junctions with very low permeability to solutes and hydrophilic molecules [36,37]. Although brain metastasis can be initiated without compromising the BBB, an impairment in the BBB has been reported in cancer patients who developed metastasis to the brain [38]. DHA has been shown to play a role in maintaining the integrity of the BBB. These observations suggest that DHA deficiency creates a permissive environment for brain tumor growth and/or helps tumors metastasize to the brain from other primary sites, such as the breast, whereas improving the DHA concentration in the brain may protect the brain from tumor development as well as brain metastasis from other organs.

DHA is stably incorporated in brain phospholipids, as it has a half-life of 2.5 years. The brain consumes about 4.5 mg DHA/day. DHA is not synthesized in the brain. Rather, it is taken up as a preformed molecule from circulation. The human liver has a limited ability to elongate Linolenic Acid (LA), an omega-3 fatty acid present in plants nuts, to DHA at a slow rate, and this is enough to maintain DHA concentrations in the brain [39]. This conversion rate can increase during certain conditions, particularly in women during pregnancy and lactation to meet fetal and newborn requirements [40]. Vegetarians on a plant-based diet get enough LA to maintain their brain DHA despite having low serum DHA levels. Ironically, the DHA concentration in plasma is not a reliable marker for DHA levels in the brain—unless there is quite a large reduction in plasma DHA arising from long-term deficiency [41]. However, a low n-3 PUFA concentration in plasma caused by nutritional deprivation can alter the concentration in the brain and its turnover, as well as altering brain function. Abnormal DHA concentrations in the brain have been linked to several human disorders [42-44]. The development and progression of cancer to brain metastasis occurs over a period of time, and it is likely that cancer patients with persistently reduced plasma DHA levels may have reduced brain DHA content. Conversely, a diet enriched by DHA, when DHA is accumulated slowly and over time, has been shown to delay or prevent neuroblastomas in mice [30].To our knowledge no published study has yet investigated the status of DHA in patients with brain cancer or with metastasis to the brain from other sites. Based on current findings, we hypothesize that a reduced DHA concentration in the brain provides a permissive environment for cancer cells to metastasize into brain tissues. Clearly, there is a need to investigate DHA's role in metastasis, particularly in the brain. Correcting the DHA concentration may dampen brain AA metabolism and create less permissive conditions for metastases.

Maintaining the DHA concentration in the brain would provide a low-cost therapeutic approach with a potentially high reward and minimal risk to cancer patients. Several reports suggest that the increased prevalence of brain metastasis from Her-2+ breast cancer is due to improved systemic therapy for stage IV breast cancer with trastuzumab, an anti-Her-2-antibody [45-47] that is effective for primary tumors and systemic metastases but ineffective for brain metastases (Her-2 Paradigm). Elevating the DHA concentration in these patients may give them hope that complete elimination of systemic and metastatic tumors is achievable, allowing them to live cancer free for longer periods, or perhaps the rest of their lives. In conclusion, it is evident that DHA and its metabolites have a role in preventing brain tumors. Further investigation in this area will be very valuable in elucidating a mechanism through which DHA and its metabolism regulate important brain functions and prevent initiation and progression of primary and/or metastatic tumors in the brain.

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