The role of omega-3 fatty acids in adult hippocampal neurogenesis

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Abstract: *Neurogenesis occurs in limited areas of the adult mammalian brain, and has been reported in the hippocampus of rodents and man. Neurogenesis is enhanced in conditions associated with enhanced synaptic plasticity and following neuronal injury, suggesting a role for neurogenesis in cognition and brain repair. Omega-3 polyunsaturated fatty acids (PUFAs) have been shown to promote hippocampal neurogenesis in a variety of models. Importantly, recent work has shown that the* fat-1 *transgenic mouse, an animal model of endogenous omega-3 PUFA enrichment, exhibits enhanced neurogenesis, with concomitant improvements in spatial memory compared to wild type mice. During ageing, the rate of neurogenesis declines significantly and there is a strong correlation between memory impairment in hippocampal-dependent tasks and this decline. Interestingly, there is a strong correlation between omega-3 PUFA and hippocampal-dependent memory tasks, and we have recently shown that supplementation of aged rats with omega-3 PUFAs partially reverses the age-related decline in neurogenesis. Thus omega-3 PUFAs positively influence neurogenesis, and these effects may contribute to improved cognitive performance. However, the mechanisms by which omega-3 PUFAs regulate neurogenesis remain unclear, although a number or putative targets have been suggested. The aims of this paper are to review the role of omega-3 PUFA in hippocampal neurogenesis, and explore some of the potential mechanisms of action which may underlie the observed effects.*

Key words: *omega-3 polyunsaturated fatty acids, docosahexaenoic acid, neurogenesis, hippocampus*

Neurogenesis is the process of generation of new neurons from neuronal precursor cells, and was first described in adult mammals in 1965, where it was identified in rodents (Altman and Das, 1965). Adult neurogenesis has subsequently been shown to occur in two specific regions of the adult brain, the subventricular zone of the olfactory bulb and the subgranular layer of the hippocampal dentate gyrus, where is has been identified in all mammals studied to date, including man (Ehninger and Kempermann, 2008). Adult neurogenesis involves several distinct stages, beginning with the proliferation of resident neural stem and progenitor cells, followed by differentiation, migration, selection and ultimately functional integration into the pre-existing circuitry (Ehninger and Kempermann, 2008).

The rate of neurogenesis and survival of new neurons in adults are enhanced by many factors, such as, growth factors and neurotransmitters, living in an enriched environment, voluntary exercise and antidepressant treatment (Emsley *et al.*, 2005). Importantly, several lines of evidence indicate that neurogenesis plays an important role in learning, memory and neural plasticity (Yirmiya and Goshen, 2011). For example, neurogenesis increases following specific forms of learning and memory formation, there is a positive correlation between the rate of neurogenesis and hippocampal-dependent memory formation and ablation of neurogenesis induces learning and memory impairments. Furthermore, increased neurogenesis in rodents has also been described after ischaemia (Takagi *et al.*, 1999), stroke (Darsalia *et al.*, 2005) and following seizures (Parent *et al.*, 1997), and neurogenesis is also increased, in the hippocampus of patients with Alzheimer's disease (Jin *et al.*, 2004); where these increases may be an attempt at brain self-repair.

The greatest negative regulator of neurogenesis is ageing, where the rate of neurogenesis in the dentate gyrus declines significantly with ageing (Kuhn *et al.*, 1996), and there is a strong correlation between memory impairment in hippocampal-dependent tasks, such as those

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based on spatial memory, and this age-related decline (Drapeau *et al.*, 2003), suggesting a link between decreased neurogenesis and memory impairments.

Overall, adult hippocampal neurogenesis has been shown to be important in learning and memory in a variety of paradigms, linking neurogenesis to both normal brain function and disease. This raises the intriguing possibility that treatments that enhance the rate of neurogenesis and survival of new neurons in adults may have a potential therapeutic role in the treatment of neurodegenerative and psychiatric disorders. This review provides an overview of the effects of omega-3 polyunsaturated fatty acids (PUFAs) in adult neurogenesis in the dentate gyrus region of the hippocampus, and explores some of the potential mechanisms of action which may underlie the observed effects.

Omega-3 PUFAs and adult hippocampal neurogenesis

Omega-3 PUFAs have an essential role in brain development and function (Innis, 2007) and beneficial effects of omega-3 PUFA treatment have consistently been demonstrated in a variety of hippocampal-dependent tasks. For example, omega-3 PUFAs enhance spatial memory tasks in adult and old rats (Gamoh *et al.*, 2001; Gamoh *et al.*, 1999, possess antidepressant effects (Freeman, 2009), increase synaptogenesis (Cao *et al.*, 2009) and enhance hippocampal neurite outgrowth (Calderon and Kim, 2004). However, the mechanisms underlying these effects are still unclear. Omega-3 PUFAs have been shown to influence developmental neurogenesis, where several studies have reported that omega-3 PUFA deficiency in embryonic and newborn rats leads to decreased neurogenesis and delay or inhibition of normal development (Coti Bertrand *et al.*, 2006; Yavin *et al.*, 2009; Kawakita *et al.*, 2006). It may therefore be hypothesised that omega-3 PUFA may enhance hippocampal function via effects on adult neurogenesis.

The first published evidence of omega-3 PUFAs enhancing adult hippocampal neurogenesis was provided by Kawakita and co-workers (Kawakita *et al.*, 2006). In this study adult rats were fed docosahexaenoic acid (DHA) at 300 mg/kg for seven weeks. DHA treatment significantly increased the number of BrdU positive and NeuN positive newborn neurons in dentate gyrus, indicating enhanced neuronal proliferation and maturation. In the second part of the study, neural stem cells were cultured under differential conditions with or without DHA for 4 and 7 days. DHA significantly increased the number of Tuj1-positive neurons compared with the control groups on both culture days, and the newborn neurons in the DHA group were morphologically more mature than in the control group. DHA also significantly decreased the incorporation ratio of BrdU during the first 24 h period; it also significantly decreased the number of pyknotic (degenerating) cells on day 7, indicating that DHA promotes the differentiation of neural stem cells into neurons by promoting cell cycle exit and suppressing cell death.

The *fat-1* transgenic mouse expresses the *fat-1* gene from *Caenorhabditis elegans*, which encodes an omega-3 desaturase, and is therefore able to convert omega-6 to omega-3 PUFAs, and is thought to model the effects of dietary enrichment with omega-3 PUFA (Kang *et al.*, 2004). *Fat-1* mice have increased brain DHA content compared with wild type litter mates. Importantly they also have significantly enhanced hippocampal neurogenesis, with an increased number of proliferating neurons and neuritogenesis, as evidenced by increased density of dendritic spines of CA1 pyramidal neurons in the hippocampus (He *et al.*, 2009). They also exhibit a better spatial learning performance in the Morris water maze compared with wild type littermates, suggesting the positive effects on neurogenesis by omega-3 PUFAs may contribute to improved cognitive performance.

Positive effects of omega-3 PUFA treatment have also been reported in the lobster brain, a model of adult neurogenesis, where short-term omega-3 PUFA dietary enrichment significantly upregulates neurogenesis (Beltz *et al.*, 2007). Taken together, these observations strongly support enhancing effects of omega-3 PUFAs on adult neurogenesis and neuritogenesis, and also suggest that this effect may be a potential mechanism underlying the beneficial effects observed on hippocampal-dependent functions. A number of putative targets have been suggested for the positive effects of omega-3 PUFA on neurogenesis.

Mechanisms of action

Adult neurogenesis occurs in a complex microenvironment and the progression from neural stem cells to mature neurons is subject to tightly coordinated control by a multitude of cell- extrinsic and intrinsic factors (Johnson *et al.*, 2009; Mu *et al.,* 2010). Extrinsic factors which have previously been shown to be modifiable by omega-PUFA treatment include glutamatergic signalling and neurotrophic factors, whereas intrinsic factors include a variety of transcription factors. The effects of omega-3 PUFAs on these regulatory factors in adult hippocampal neurogenesis have begun to be explored.

Brain-derived neurotrophic factor (BDNF), a neurotrophin involved in spatial learning and memory, plays an important role in dietary restriction-induced neurogenesis (Lee *et al.*, 2002). Several studies have reported enhanced hippocampal neurogenesis in parallel with increase levels of BDNF levels following omega-3 PUFA treatment (Cysneiros *et al.,* 2010; Venna *et al.*, 2009; Blondeau *et al.*, 2009). For example, three sequential injections of α-linolenic acid significantly enhances adult hippocampal neurogenesis in mice, and increases in the expression of BDNF in hippocampal neurons and cortical and hippocampal tissue (Blondeau *et al.*, 2009). In this study, the treatment also significantly increases the expression of proteins critical for synaptogenesis and synapse function, syntophysin-1, VAMP-2 and SNAP-25, and proteins supporting glutamatergic neurotransmission, V-GLUT-1 and V-GLUT-2. These studies therefore indicate that the positive effects of omega-3 PUFA on neurogenesis may at least in part be mediated via effects on BDNF expression.

There is strong evidence indicating the importance of the retinoic acid receptor family of transcription factors in regulating neural plasticity and neurogenesis in the hippocampus (Mccaffery *et al.*, 2006; Jacobs *et al.*, 2006). Furthermore, retinoic acid receptor agonists enhance BDNF expression (Katsuki *et al.*, 2009), and are involved in the induction of neural progenitor cells to become doublecortin-expressing cells (Goncalves

et al., 2009). Doublecortin is a microtubule associated protein associated with neuronal differentiation and migration. Dietary supplementation of aged rats with an omega-3 PUFA enriched diet for 12 weeks partially reverses the age-related decline in neurogenesis in the dentate gyrus, as assessed by doublecortin expression, with a concomitant reversal of the age-related decreases in retinoic acid receptor-α (RARα) and retinoid X receptor-β (RXRβ) expression in the dentate gyrus (Dyall *et al.*, 2010). It remains to be established if the effects of omega-3 PUFA on neurogenesis are directly linked to the restoration of retinoid signalling in ageing; however, it is likely that omega- PUFAs possess cell-intrinsic effects mediated by actions at transcription factors.

In neural stem cells, neurogenesis is regulated by activator-type and repressor-type basic helix-loop-helix (bHLH) transcription factors (Johnson *et al.*, 2009; Mu *et al.*, 2010). Neurogenesis is promoted by activator-type bHLH transcription factors, such as neurogenin, NeuroD and Ascl1 (also known as Mash1), whereas, hairy and enhancer of split 1 and 5 (Hes1 and Hes5) prevent terminal differentiation and preserve a pool of stem cells. An interesting recent study has investigated the effects of DHA treatment on the expression of these bHLH transcription factors in neural stem cells (Katakura *et al.*, 2009). DHA treatment significantly decreased the expression of Hes1 and increased neurogenin1 and NeuroD. MAP2 expression, a neuron specific protein, was also significantly increased. Since MAP2 is activated by NeuroD and repressed by Hes1, these results suggest that DHA stimulates neuronal differentiation by altering the balance of these bHLH transcription factors. However, the mechanisms by which DHA alter the expression of these transcription factors remain to be established.

It should also be noted that calorific or dietary restriction have been shown to closely relate to hippocampal neurogenesis (Lee *et al.*, 2000). For this reason, in our study we monitored the food intake and weight of the animals throughout both the mixed omega-3 PUFA and DHA treatments (Dyall *et al.*, 2010). In both studies, the omega-3 PUFA treated animals ate a similar amount of food to the control and untreated old animals, and indeed there was even a small non-significant increase in the average weight of the omega-3 PUFA treated animals compared to the other groups, indicating dietary restriction was not a factor in the observed effects on neurogenesis.

In summary, omega-3 PUFA treatment has consistently been shown to enhance adult hippocampal neurogenesis in a variety of animal models. Elucidating the mechanisms for this effect has been complicated by the convergent pathways involved in regulating neurogenesis and the pleiotropic effects of omega-3 PUFAs. However, a number of potential targets have been identified. This article has briefly reviewed some of the evidence of effects on cell-extrinsic and intrinsic regulatory factors by omega-3 PUFAs. These include, iinfluencing neurotrophin levels, such as BDNF, modulation of transcription factors, such as retinoid receptors and the bHLH transcription factors. However, the effects of omega-3 PUFA are undoubtedly mediated by further mechanisms, which may include biophysical effects in neuronal membranes, modulation of pro-inflammatory cytokine levels, and interaction with cannabinoid signalling pathways. In order for omega-3 PUFA to achieve their therapeutic potential it is imperative to understand the molecular mechanisms that mediate their observed effects, and understanding their regulatory effects neurogenesis is an important avenue for exploration.

REFERENCES

Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J Comp Neurol* 1965; 124: 319-35.

Beltz BS, Tlusty MF, Benton JL, Sandeman DC. Omega-3 fatty acids upregulate adult neurogenesis. *Neurosci Lett* 2007; 415: 154-8.

Blondeau N, Nguemeni C, Debruyne DN, *et al.* Subchronic alpha-linolenic acid treatment enhances brain plasticity and exerts an antidepressant effect: a versatile potential therapy for stroke. *Neuropsychopharmacology* 2009; 34: 2548-59.

Calderon F, Kim HY. Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *J Neurochem* 2004; 90: 979-88.

Cao D, Kevala K, Kim J, *et al.* Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. *J Neurochem* 2009; 111: 510-21.

Coti Bertrand P, O'kusky JR, Innis SM. Maternal dietary (n-3) fatty acid deficiency alters neurogenesis in the embryonic rat brain. *J Nutr* 2006; 136: 1570-5.

Cysneiros RM, Ferrari D, Arida RM, *et al.* Qualitative analysis of hippocampal plastic changes in rats with epilepsy supplemented with oral omega-3 fatty acids. *Epilepsy & Behavior* 2010; 17: 33-8.

Darsalia V, Heldmann U, Lindvall O, Kokaia Z. Stroke-induced neurogenesis in aged brain. *Stroke* 2005; 36: 1790-5.

Drapeau E, Mayo W, Aurousseau C, Le Moal M, Piazza PV, Abrous DN. Spatial memory performances of aged rats in the water maze predict levels of hippocampal neurogenesis. *Proc Natl Acad Sci U S A* 2003; 100: 14385-90.

Dyall SC, Michael GJ, Michael-Titus AT. Omega-3 fatty acids reverse age-related decreases in nuclear receptors and increase neurogenesis in old rats. *Journal of Neuroscience Research* 2010; 88: 2091-102.

Ehninger D, Kempermann G. Neurogenesis in the adult hippocampus. *Cell Tissue Res* 2008; 331: 243-50.

Emsley JG, Mitchell BD, Kempermann G, Macklis JD. Adult neurogenesis and repair of the adult CNS with neural progenitors, precursors, and stem cells. *Prog Neurobiol* 2005; 75: 321-41.

Goncalves MB, Agudo M, Connor S, *et al.* Sequential RARbeta and alpha signalling in vivo can induce adult forebrain neural progenitor cells to differentiate into neurons through Shh and FGF signalling pathways. *Dev Biol* 2009; 326: 305-13.

Freeman MP. Omega-3 fatty acids in major depressive disorder. *J Clin Psychiatry* 2009; 70 (Suppl. 5): 7-11.

Gamoh S, Hashimoto M, Hossain S, Masumura S. Chronic administration of docosahexaenoic acid improves the performance of radial arm maze task in aged rats. *Clin Exp Pharmacol Physiol* 2001; 28: 266-70.

Gamoh S, Hashimoto M, Sugioka K, *et al.* Chronic administration of docosahexaenoic acid improves reference memory-related learning ability in young rats. *Neuroscience* 1999; 93: 237-41.

He C, Qu X, Cui L, Wang J, Kang JX. Improved spatial learning performance of fat-1 mice is associated with enhanced neurogenesis and neuritogenesis by docosahexaenoic acid. *Proc Natl Acad Sci U S A* 2009; 106: 11370-5.

Innis SM. Dietary (n-3) fatty acids and brain development. *J Nutr* 2007; 137: 855-9.

Jacobs S, Lie DC, Decicco KL, *et al.* Retinoic acid is required early during adult neurogenesis in the dentate gyrus. *Proceedings of the National Academy of Sciences of the United States of America* 2006; 103: 3902-7.

Jin K, Peel AL, Mao XO, *et al.* Increased hippocampal neurogenesis in Alzheimer's disease. *Proc Natl Acad Sci U S A* 2004; 101: 343-7.

Johnson MA, Ables JL, Eisch AJ. Cell-intrinsic signals that regulate adult neurogenesis in vivo: insights from inducible approaches. *BMB Rep* 2009; 42: 245-59.

Kang JX, Wang J, Wu L, Kang ZB. *Fat*-1 mice convert n-6 to n-3 fatty acids. *Nature* 2004; 427: 504.

Katakura M, Hashimoto M, Shahdat HM, *et al.* Docosahexaenoic acid promotes neuronal differentiation by regulating basic helix–loop–helix transcription factors and cell cycle in neural stem cells. *Neuroscience* 2009; 160: 651-60.

Katsuki H, Kurimoto E, Takemori S, *et al.* Retinoic acid receptor stimulation protects midbrain dopaminergic neurons from inflammatory degeneration via BDNF-mediated signaling. *J Neurochem* 2009; 110: 707-18.

Kawakita E, Hashimoto M, Shido O. Docosahexaenoic acid promotes neurogenesis *in vitro* and *in vivo*. *Neuroscience* 2006; 139: 991-7.

Kuhn Hg, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J Neurosci* 1996; 16: 2027-33.

Lee J, Duan W, Long JM, Ingram DK, Mattson MP. Dietary restriction increases the number of newly generated neural cells, and induces BDNF expression, in the dentate gyrus of rats. *J Mol Neurosci* 2000; 15: 99-108.

Lee J, Duan W, Mattson MP. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *J Neurochem* 2002; 82: 1367-75.

Mccaffery PJ, Zhang J, Crandall JE. Retinoic Acid Signaling and Function in the Adult Hippocampus. *J Neurobiol* 2006; 66: 780-91.

Mu Y, Lee SW, Gage FH. Signaling in adult neurogenesis. *Curr Opin Neurobiol* 2010; 20: 416-23.

Parent JM, Yu TW, Leibowitz RT, Geschwind DH, Sloviter RS, Lowenstein DH. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 1997; 17: 3727-38.

Takagi Y, Nozaki K, Takahashi J, Yodoi J, Ishikawa M, Hashimoto N. Proliferation of neuronal precursor cells in the dentate gyrus is accelerated after transient forebrain ischemia in mice. *Brain Res* 1999; 831: 283-7.

Venna VR, Deplanque D, Allet C, Belarbi K, Hamdane M, Bordet R. PUFA induce antidepressant-like effects in parallel to structural and molecular changes in the hippocampus. *Psychoneuroendocrinology* 2009; 34: 199-211.

Yavin E, Himovichi E, Eilam R. Delayed cell migration in the developing rat brain following maternal omega 3 alpha linolenic acid dietary deficiency. *Neuroscience* 2009; 162: 1011-22.

Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain Behav Immun* 2011; 25: 181-213.