Review Article

The role of eicosanoids in the brain

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The brain contains two main polyunsaturated fatty acids (PUFA), arachidonic acid (AA) and docosahexaenoic acid (DHA). These PUFA are located almost exclusively in the *sn*2-position of phosphoglycerides which are found in the neural cell membranes. Liberation of these PUFA from the phosphoglycerides occurs via the action of specific phospholipases (PLA_2). Free AA can be metabolised by cyclooxygenases to prostaglandins and thromboxane, while both AA and DHA can be metabolised by lipoxygenases to form hydroxy derivatives and leukotrienes. AA is also metabolised to lipoxins via the 5-lipoxygenase pathway. The eicosanoids formed play important roles in neural function including sleep induction (PGD_2), long term potentiation, spatial learning and synaptic plasticity (PGE_2), resolution of inflammation (lipoxins) and anti-inflammatory and neuroprotective bioactivity (dihydroxy-docosatriene, neuroprotectin D_1, formed from DHA). COX-inhibitors have been shown to reduce oxidative stress and cognitive impairment. Additionally, drugs which are used to treat depression have been shown to reduce the turnover of AA to PGE_2 in the brain. Diets deficient in omega 3 PUFA lead to reduced DHA in the brain and increased turnover of AA to eicosanoids, an effect which is overcome by restoring the omega 3 PUFA to the diet. In neural trauma and neurodegenerative diseases, there is a dramatic rise in the levels of AA-derived eicosanoids. In contrast, DHA-derived compounds can prevent neuroinflammation. Clearly, the eicosanoids are very important for the normal functioning of the brain, while the PUFA themselves are important in membrane structure and function.

Key Words: eicosanoids, docosanoids, polyunsaturated fatty acids, brain, arachidonic acid, docosahexaenoic acid

INTRODUCTION

The brain has the second highest content of lipids in the human body next to adipocytes, at 36-60%. Brain lipids are far more complex than adipose lipids and consist of glycerophospholipids, sphingolipids, gangliosides and cholesterol, with little or no triglycerides and cholesterol esters. Metabolites of the glycerophospholipid polyunsaturated fatty acids (PUFA) have been implicated in neuroinflammation and depression. Glycerophospholipids are composed of two fatty acids attached to a glycerol backbone. A saturated fatty acid is usually found in the sn-1 position and a PUFA in the sn-2 position and a phosphate in the sn-3 position, covalently linked to a base group (choline, serine, inositol, ethanolamine). The main brain PUFA are arachidonic acid (AA; 20:4ω6) or docosa-hexaenoic acid (DHA; 22:6ω3); these are both derived from the essential fatty acids (EFA), linoleic (LA) and alpha-linolenic acids (ALA), respectively. In grey matter, the proportion of DHA in glycerophospholipids is higher than AA, whereas in white matter this situation is reversed.[1] The brain grey matter PUFA profiles are similar in different mammals, with DHA, AA and 22:4n–6 being the three major PUFA (Fig. 1).[2]

It has been well documented that the fatty acid composition of adipose tissue in a healthy individual is indicative of the fatty acid composition of lipids in their diet. This is also true for brain fatty acid composition, however there are major differences between these two tissues. Adipose lipids are mostly triglycerides and contain very low levels of AA and DHA; brain lipids are mostly complex lipids and contain high proportions of these two long chain PUFA in the neural cell membranes. Furthermore, it is very difficult, but not impossible, to alter the fatty acid profile of the brain cell membranes; the brain DHA levels can be decreased by a dietary deficiency of omega 3 PUFA and brain AA and DHA levels are both decreased in dietary EFA deficiency.[3] The effect of omega 3 PUFA deficiency on the brain has been far more extensively characterised than that of EFA deficiency. Most importantly deficiency of brain DHA has critical effects on neuronal development and behaviour, including changes in learning, memory, auditory and olfactory responses. Brain DHA plays a crucial role in [a] membrane order (membrane fluidity);[4,5] [b] regulation of dopaminergic and serotoninergic neurotransmission;[6] [c] regulation of membrane-bound enzymes (Na/K-dependent ATP'ase);[7] [d] signal transduction via effects on inositol phosphates, diacylglycerol and protein kinase C;[8] [e]

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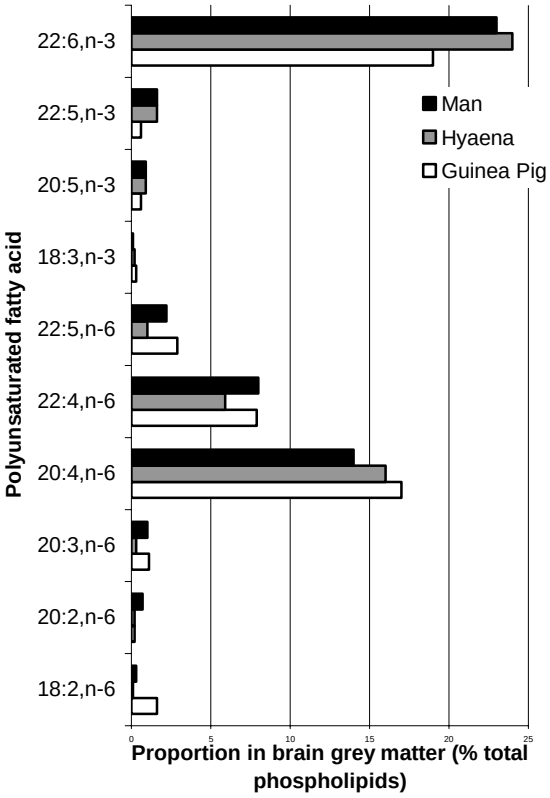

Figure 1. Similarity of brain grey matter PUFA in three different mammalian species

decreased glucose uptake;[9,10] [f] regulation of the synthesis of eicosanoids derived from arachidonic acid,[11] and as a precursor of docosatrienes and 17S resolvins,[12] novel anti-inflammatory mediators;[13] [g] involvement in the growth of neuronal cells and the protection of cells from apoptosis[14-17] and [h] regulation of gene expression of many different genes in rat brain (for review see, Sinclair et al 2002).[18] There has been far less research on the role of brain AA, partly because it is almost impossible to deplete brain AA levels by dietary deficiency studies. Clearly, brain AA is important as a precursor of a wide range of eicosanoids and leukotrienes which play critical roles in many aspects of neural function, as will be seen in this review.

Under the control of specific stimuli, PUFA are released from the glycerophospholipids by the action of various phospholipases (cytosolic phospholipase AII, $cPLA_2$; plasmalogen selective phospholipase AII, PlsEtn-PLA_2 and secretory phospholipase AII, $sPLA_2$)[19] and metabolised by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes into a variety of oxygenated PUFA derivatives known as eicosanoids (prostaglandins, thromboxanes, lipoxins, leukotrienes, hydroxyeicosatetraenoic and epoxyeicosatetraenoic acids), and docosatrienes (neuroprotectins and resolvins) which are locally acting hormone-like compounds as shown in Figure 2. As discussed later, COX is involved in the production of pro-inflammatory metabolites of AA, including prostaglandins and thromboxanes and leukotrienes (from AA via the LOX pathway). LOX on the other hand generates anti-inflammatory DHA-derived metabolites and lipoxins derived from AA via the 5-LOX pathway (Fig. 2). COX-1 is constitutively expressed in the body and acts as a "housekeeping" enzyme.[19,20] COX-2 is an inducible enzyme under stress conditions, such as inflammation.[19,20] Asprin and ibuprofen are non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit the metabolism of AA by COX enzymes to eicosanoids. These drugs have been used to prevent inflammation and recently been implicated as a potential therapeutic for neurodegenerative disease.[21-23]

Extensive literature searching has revealed the numerous roles that metabolites of DHA and AA play in neural cells. In this paper we discuss the role of eicosanoids and docosanoids in sleep, memory, inflammation and neuropsychiatric disorders. We also briefly discuss how dietary alterations and drug therapy may influence their actions.

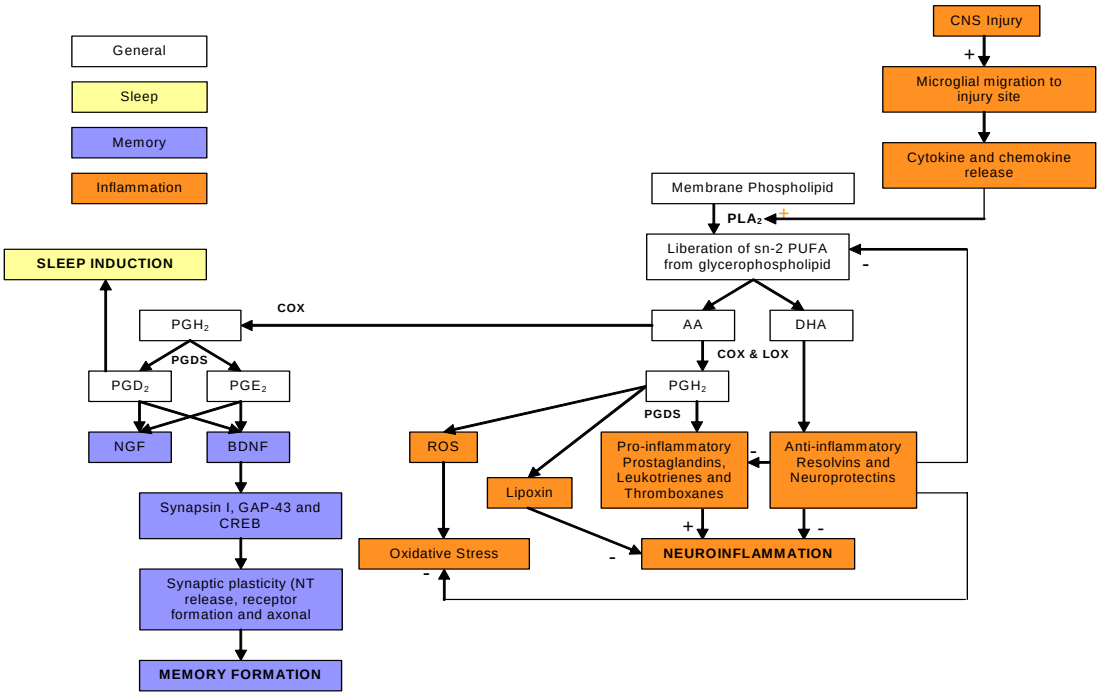

Figure 2. Overview of the actions of eicosanoids and docosanoids in sleep induction, memory formation and inflammation

ESSENTIAL FATTY ACID FORMATION, INTEGRATION IN NEURONAL TISSUE AND METABOLISM

Alpha-linolenic acid and linoleic acid are EFA and the precursors of the longer chain PUFA eicosapentaenoic acid (EPA) and DHA, and AA, respectively. The rate of conversion of dietary ALA to DHA in the body is very low.[24] The rate of conversion of LA to AA has been difficult to determine although some sources state it to be less than 5% which is as much as 10x greater than ALA to DHA conversion.[25] The rate of conversion of the EFA to their C20 and C22 fatty acid metabolites may be affected by age, stress, immune state and sex differences.[25] Smoking and alcohol also affect EFA conversion rate. Alcohol consumption significantly decreases levels of DHA in the feline brain and increases the levels of omega-6 derived PUFA.[26] Smoking appears to have the opposite effect. Smoking has been found to increase the bioavailability of omega 3 PUFA. One possible mechanism is via increased absorption by the gut. However, it is more likely that this is achieved through a compensatory mechanism where the body increases endogenous transformation of omega 3 PUFA to DHA. This compensates for the PUFA lost to oxidation by free radicals which are found in higher levels in smokers.[27]

SLEEP

Sleep is necessary for health and survival. Without sufficient regular rest periods, mental and physical deficits arise including lack of concentration and motivation, muscle aches and visual anomalies. Sleep is characterised by cyclic phases that are measured through eye movement. Rapid eye movement sleep (REM) is a period where the brain is active and muscle tone is absent from the body; it is often associated with dreaming. In non-rapid eye movement (NREM) sleep, cerebral activity is minimal and muscle tone is present. Postural changes are seen during this period.[28] Prostaglandin D_2 (PGD_2) has been shown to play an important role in sleep regulation and memory formation (Fig. 3).

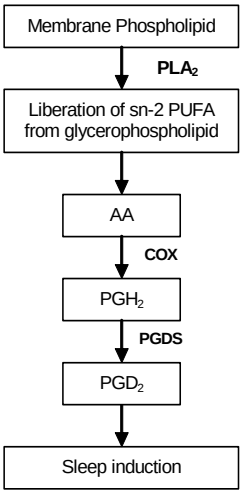

Figure 3. Scheme outlining the formation of PGD_2 from AA

There is a circadian clock-dependent PGD_2 fluctuation in cerebrospinal fluid. Rats exhibit a higher concentration of PGD_2 during the day when they are sleeping than at night when they are awake.[29] The brain upregulates PGD_2 production under sleep deprivation conditions in an attempt to induce sleep. Results from animal experiments have exhibited a dose-dependent relationship between PGD_2 and increased sleep time.[30] Both NREM and REM were induced by intracerebroventricular infusions of PGD_2 in mice, rats and monkeys.[31] Likewise, inhibition of PGD_2 formation through the introduction of selenium tetrachloride, a selective inhibitor of PGD_2 synthase, in rats reduces NREM and REM sleep.[32] Other experiments involving transgenic and knockout mice have supported PGD_2's role as a sleep inducer.[33]

MEMORY AND LEARNING

Simplistically, memory can be said to exist as two types, short term (STM) and long term memory (LTM). An "event" exists in the STM before it is stored as a LTM. This shift in memory storage is the result of neuronal remodelling in the brain. DHA has been shown to promote neurite growth and remodelling in hippocampal neurons which is important as the hippocampus is the main site for memory formation.[16]

Brain derived neurotrophic factor (BDNF) activity combined with PGE_2 also regulate the synaptic plasticity. Specifically, it's their actions which induce long-term potentiation (LTP). BDNF is a potent trophic factor in the brain.[34] Synthesis of BDNF is induced by prostaglandins (Fig. 4).

In vitro experiments with mouse astrocyte cells shows PGE_2 and PGD_2 stimulate both nerve growth factor and BDNF production.[35] Kesslack et al. and Mizuno et al. found that BDNF was elevated in the hippocampus of tested rats that learned a spatial memory task.[36,37] It has

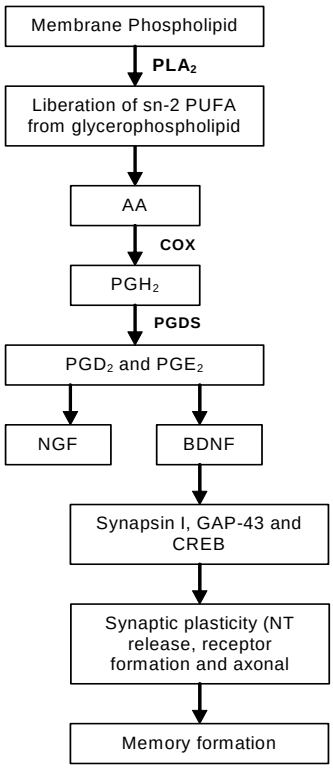

Figure 4. Scheme depicting role of eicosanoids in memory formation

also been documented that animals exhibit learning difficulties when BDNF is reduced. This occurs through BDNF modulation of synapsin I, growth associated protein 43 (GAP-43) and cyclic AMP response element-binding protein (CREB). Synapsin I action mediates axonal growth and neurotransmitter (NT) release. GAP-43 performs many of the same actions as synapsin I. CREB involvement in BDNF action is related to synaptic plasticity after neuronal insult. BDNF receptor tyrosine kinase receptor B (trkB) also plays an important role in memory.[38] Spatial learning induces phosphorylation of the receptor.

Modification at several sites in the memory signalling cascade has supported the theory that PUFA are important for memory. Rodent experiments showed that BDNF was important, not only for memory formation, but also for retention.

1. n–3 PUFA deficiency impairs hippocampal-dependent learning and memory[39, 40]
2. PLA_2 - inhibition in rat hippocampus impairs STM and LTM[41]
3. Broad spectrum cyclooxygenase inhibitor - impairs LTP and spatial learning capacity in rats[23]
4. COX-2 - selective inhibitors NS392 and nimesulide reduce LTP. This can be restored by the addition of PGE_2[42]
5. BDNF - reduction through genetic manipulation of BDNF gene produced mice that exhibit learning difficulties[43]
6. TrkB - inhibition of tyrosine kinase activity in rats delays memory acquisition[38]

NEUROINFLAMMATION

Inflammation involves the coordination of several molecular events whose purpose is to protect the affected tissue from damage. This is usually characterised by a physical change in an affected tissue, including heat, colour (red), swelling, pain and tenderness. Functional anomalies may also be attributed to inflammation in some cases. Neuroinflammation can be associated with both neurological injury and neurological disease. Neurological injury can be brought about through invasive injury of the neural tissue, neurotoxins, bacterial or viral infiltration of the neural tissue or ischemia-reperfusion (IR) injury.[44] Alzheimer's disease (AD), multiple sclerosis (MS) and epilepsy are all diseases with neuroinflammatory characteristics.[19] Beta-amyloid plaques and neurofibrillary tangles are characteristic of AD and are the likely cause of the associated neuroinflammation. Long-term treatment with anti-inflammatory drugs has been shown to (a) reduce the risk of developing AD, (b) delay its onset and (c) slow its progression most probably through preventing or reducing chronic inflammation.[45]

Shortly after an insult to neural tissue, a rapid cascade of molecular events takes place to initially potentiate and then, in most cases, reduce the inflammatory response (Fig. 5). This begins with the migration of microglial cells and adhesion of leukocytes to the affected site. Microglial cells are responsible for the production of many cytokines, including tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), and chemokines as well as vascular cell adhesion molecule-1 (VCAM-1) and intracellular cell adhesion molecule-1 (ICAM-1). The consequence of this increase in cytokine and chemokine production is a widely observed increase in PLA_2 activity.[46] Inflammation induced through bacterial lipopolysaccharide (LPS) infusion increases secretory PLA_2A (sPLA IIA) activity, which is a non-selective phospholipase that hydrolyses

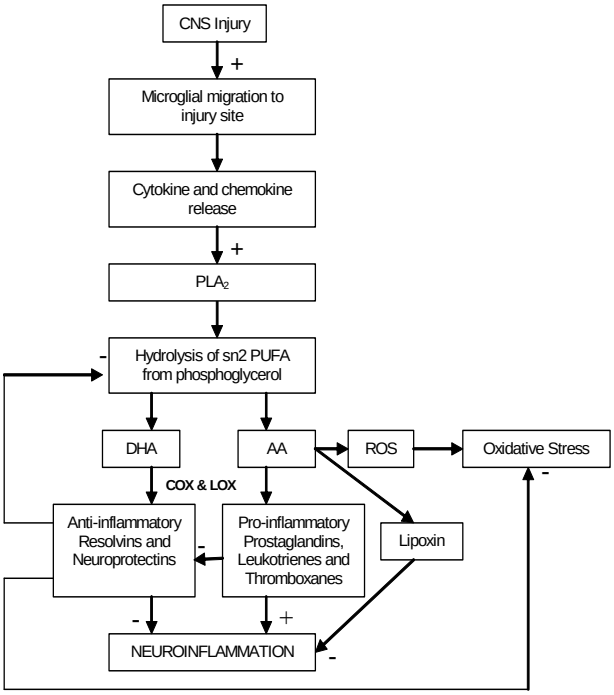

Figure 5. Scheme showing the role of eicosanoids and docosanoids in neuroinflammation

both AA and DHA. Ca^{2+} influx associated with IR also stimulates PLA_2 activity leading to an increase in free AA and/or DHA.[46,47] Increases of PLA_2 activity have also been determined through measurement of free fatty acids (FFA) in cerebrospinal fluid (CSF) following neural trauma. For up to 48 hours following traumatic brain injury (TBI), levels of AA, DHA, LA and ALA are all significantly elevated in CSF. The concentration of these FFA normalise around 96 hours after the initial injury. Further analysis of the data showed a correlation between the severity of the TBI with the level of FFA in the CSF.[48]

Following neural injury, the prostaglandins released are generally classed as exhibiting pro-inflammatory effects. Leukotrienes and thromboxanes elicit a vascular response (both are potent vasoconstrictors). Stroke results in an increase in both 5-LOX activity and leukotriene levels.[49] Other actions of leukotrienes include mediating chemotaxis of leukocytes and disruption of the blood brain barrier. They also increase free radical production as well as potentiating cytokine production.[22]

Lipoxins, also derived from AA, promote resolution of inflammation through a G-protein-coupled receptor leading to expression of a cytokine signalling inhibitor (SOCS-2).[50] Mice deficient in SOCS-2 demonstrate uncontrolled production of pro-inflammatory cytokines and increased mortality. In addition to lipoxin, resolvins and neuroprotectins (from DHA) are also produced in the brain to counteract and resolve neuroinflammation. This is critical to ensure that the inflammatory response does not overwhelm the brain and cause excessive damage.

These DHA-derived molecules are collectively known as docosanoids. A recent study by Michael-Titus and colleagues found that omega 3 fatty acids improve recovery after spinal cord injury.[51] Rats injected with ALA and DHA three minutes after injury showed a significant increase in locomotor performance and neuroprotection compared with AA-injected rats. In fact, this omega-6 fatty acid appeared to potentiate damage in spinal cord injury when injected post-injury. Resolvin-type messengers (17*S*-DHA) down-regulate the microglia produced cytokines TNF-α and IL-1β. Neuroprotectin D1 (10, 17S-docosatriene, NPD1) also down-regulates cytokine production.[46]

In conjunction with this, NPD1 generates several messengers to mediate an anti-inflammatory response[44]:

1. Reduces NF-κB activation. NF-κB is a regulator of gene transcription of pro-inflammatory mediators.[52]
2. Down-regulates COX-2 thus inhibiting the production of pro-inflammatory AA derived eicosanoids.
3. Reduces pro-apoptotic Bcl-2 family members, Bax, Bad (apoptotic regulators).
4. Increases anti-apoptotic Bcl-2 and Bcl-xL (apoptotic regulators).
5. Inhibition of neuronal cell death through reduction in caspase activation (mediator of apoptosis).[12]

OXIDATIVE STRESS

Reactive oxygen species (ROS) and reactive nitrogen species (RNS), commonly referred to as free radicals, are constitutively present in the body at low levels. Oxidative stress is a state in which the production of free radicals greatly increases to the point where the intracellular mechanisms which render the ROS harmless are overwhelmed leaving the potential for the damage caused by the ROS to propagate. Regulating free radical production are several enzymes, including superoxide dismutase and catalase and antioxidants such as alpha-tocopherol. Free radicals can damage nucleic acids, protein and lipids. Alterations made to proteins, including enzymes, may lead to dysfunction and an increased susceptibility for proteolysis. DNA damage has deleterious effects as it has the potential for mutagenic replication. Lipid oxidation occurs when ROS and RNS attack bonds within the fatty acids. This oxidation propagates to other bonds along the fatty acid and to surrounding fatty acids. This is a concern especially in neural tissue as it contains a high proportion of PUFA. Free radical production does not always have a negative impact on the body. Higher organisms have incorporated free radicals into physiological signal cascades, for example, control of ventilation and vascular tone.[53]

With reference to neuroinflammation, ROS can be produced by two means. The first is by leukocytes that accumulate near the inflamed region. There is also some evidence for calcium (Ca^{2+}) induced production of ROS. These ROS have the potential to damage intracellular components including the mitochondria. This can lead to an even greater increase in ROS through interference in the electron transport chain caused by damage to electron carriers. The free radicals produced by this damage include superoxide ($O_2^{\bullet-}$), peroxide (H_2O_2) and hydroxyl ($OH^{\bullet}$) radicals. This is particularly relevant to IR injury. In the ischemic phase, oxygen and glucose deprivation cause an influx of Ca^{2+} which induces production of ROS. The reperfusion phase sees the restoration of blood flow that places further stress on the ROS defence system. Novel research conducted by Marchesalli and colleagues showed that NPD1 and 17*R*-resolvins reduced leukocyte infiltration attributed to IR injury in a mouse stroke model.[54]

DHA attenuation of oxidative stress has also been demonstrated in a TBI rat model.[55] Synaptic dysfunction and cognitive impairment are attributed to TBI. One of the causes of this apart from the insult itself is an increase in ROS degradation of membrane phospholipids. Although the exact mechanism is not known, rats on a fish oil supplemented diet displayed a significantly lower levels of oxidative damage compared with control rats.[55] Lipid peroxidation has also been implicated in neurodegenerative disease. This may be related to alterations in membrane fluidity and damage to membrane transporters that result from oxidation.[56] Abnormalities in intracellular lipid signalling may also be a consequence of oxidative damage.

In some cases, cell function ceases due to overwhelming damage from free radical attack. Each cell has a damage "threshold" level. If this is not reached then the cell will be repaired. If the extent of the damage is too great for repair, a cascade of intracellular events will unfold to induce apoptosis. Mitochondrial mediated apoptosis occurs via the mobilization of cytochrome c from the inner mitochondrial membrane via the Bax protein.[57] This is facilitated by ROS. With increased amounts of cytochrome c released there is a higher probability of subsequent activation of caspases-9 and -3. This increases the likelihood of apoptosis of dopaminergic neurons. Caspase-3 activation is reduced in an environment where omega-3 PUFA are in abundance. Neuro 2A cells enriched with phosphatidylserine, which is high in DHA, were shown to have decreased levels of apoptotic cell death, induced by deprivation of serum.[58] This finding has important implications for neurodegenerative diseases which result from anomalies in programmed cell death.

DEPRESSION AND OTHER NEUROPSYCHIATRIC DISORDERS

In the past studying the causes of neuropsychiatric disorders has proved difficult due to the broad spectrum of symptoms and the difficulty of accurate diagnosis. Neuropsychiatric disorders are thought to result from a combination of genetic and environmental stimuli (Figure 6). Dietary PUFA intake has been implicated as being associated with many neuropsychiatric disorders including depression, schizophrenia, AD, Attention Deficit Hyperactivity Disorder (ADHD), dyslexia and autism.[25,59] In conjunction with inadequate dietary intake, abnormalities in membrane phospholipid metabolism are also thought to cause or potentiate neuropsychiatric disease.[25]

Although the pathogenesis of depression is not well defined there is a surprisingly wide range of therapies and pharmaceuticals available for treatment. This can be attributed to the serendipitous discovery of anti-depressant medication in the 20th century. It is now known that NT release, brain glucose metabolism, AA metabolism, pro-inflammatory cytokines, BDNF and neuronal atrophy are

all associated with depression.[60] Several classes of anti-depressants specifically inhibit reuptake of the NTs serotonin and noradrenaline in the brain to increase the amount available for receptor binding.[61] It has been suggested that depression is associated with an immune response. As outlined above (see neuroinflammation), the release of pro-inflammatory cytokines is seen in neuroinflammation. Tricyclic anti-depressants inhibit cytokine release. TNF-α, IL-1β and IL-6 have all been shown to decrease with administration of anti-depressants.[62] TGF-β1 and IL-12 have also been shown to decrease with treatment.[63] Furthermore it has been noted that patients undergoing certain treatments which require cytokine administration, such as cancer and hepatitis C therapies, become symptomatic for depression.[64]

Impairment of neurotrophic mechanisms is a very active avenue of neuropsychiatric disorder research. Changes in neuronal plasticity are of particular interest. It appears that variations in the levels of CREB and BDNF are related to the development of depression. Brain expression levels of BDNF are influenced by environmental states, such as stress, exercise and diet. Stress increases glucocorticoid levels which reduce BDNF levels.[61] Chronic administration of antidepressants can not only normalise BDNF in the brain, but also increase the expression of the BDNF receptor trkB.[61,65-67] Additionally pre-administration of anti-depressants prevents stress-induced decrease in BDNF.[68] It has also been hypothesised that chronic stress-induced depression may result in neuronal atrophy and death. Theoretically, given the neurotrophic effects of BDNF in mediating neuronal growth and synaptic plasticity, BDNF could act to reverse this. As it is not yet possible to measure BDNF in brain tissue of living human sufferers, a novel study introduced the idea of a possible correlation between serum BDNF levels and degree of depression. The treatment group composed of depression patients treated with antidepressants had significantly higher levels of BDNF compared with depression patients with no treatment. They also found a correlation between BDNF levels and the degree of severity of depression in all patients.[65] This is significant as it introduces the possibility for clinical molecular marker for depression.

BDNF expression is also partly mediated by CREB (see Fig. 6). There is a strong correlation between BDNF and CREB region specific expression in the brain. Chronic administration of anti-depressants upregulates CREB.[68] Post-mortem examination of patients taking antidepressants at time of death identified increased levels of temporal cortex CREB compared with those not on medication. It appears that the effect CREB has on depression is not entirely due to an overall increase in CREB as some antidepressants reduce CREB in some parts of the brain and achieve the same effect.[69] This suggests that the role of CREB in depression is region specific. The mechanisms involved in the increase in CREB production by antidepressants have been reviewed by Vaidya and Duman.[68]

Ultimately, increased activation of CREB leads to increased levels of BDNF resulting in neurotrophic effects including increased neuronal survival and function, and changes in structural plasticity. Interestingly, BDNF levels can be increased by exercise and specific dietary components such as omega 3 PUFA and decreased with a diet containing saturated fat and refined sugar.[70-72] One study

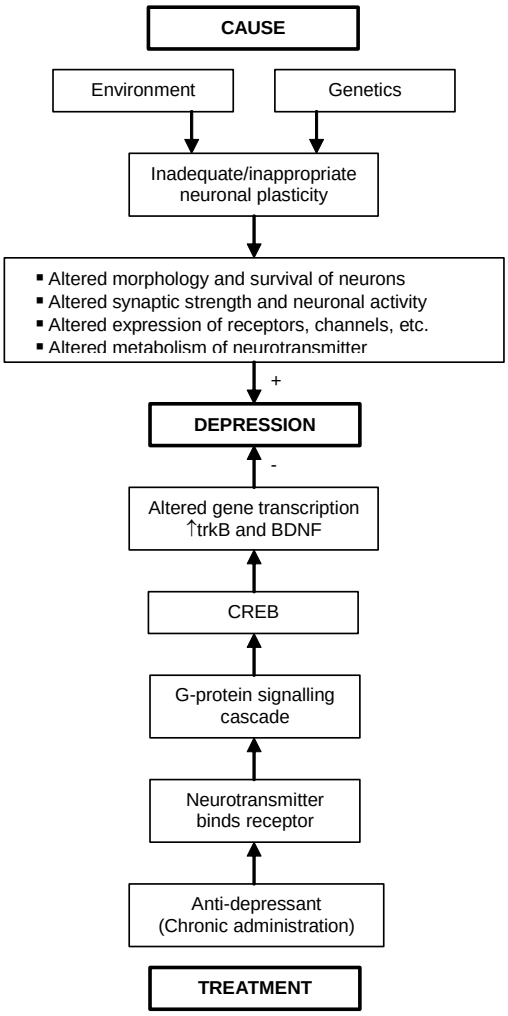

Figure 6. Overview of the actions of the role of CREB in depression.

in rats consuming a diet high in saturated fat and refined sugar showed decreased level of BDNF mRNA and protein in the hippocampus.[72] This reduction in BDNF was associated with impairment in spatial learning ability. This is a significant finding as exercise and dietary changes may be a safer alternative treatment to drugs when treating mild cases of depression, as they will not produce unwanted side effects.

Recent data in rats from Rapoport's group revealed that the drugs commonly used to treat bipolar disorder, lithium, carbamazapine and valproic acid, significantly reduce AA turnover in the brain.[73-75] This new information reveals the possibility of another explanation for the benefit seen from using omega 3 PUFA in mood disorders, given that the omega 3 PUFA competitively inhibit the metabolism of AA to eicosanoids and leukotrienes. Rats treated with lithium and carbamazapine demonstrated a reduced turnover of AA, but not DHA, in brain phospholipids and decreased mRNA, protein levels and enzyme activity of a cytosolic phospholipase A_2, which is AA-specific.[74,75] This treatment also reduced the brain concentration of prostaglandin E_2, a product of the COX pathway presumably due to reduced release of AA from the phospholipids.[76] It is possible that EPA is effective in depression through its ability to inhibit COX activity, although the

levels of EPA in the brain phospholipids are very low. The same group showed that another drug used in treating bipolar disorder, valproic acid, also reduced AA turnover in the brain but by a different mechanism, namely the inhibition of the formation of arachidonoyl CoA.[77] It is of interest that two further papers from this group demonstrate effects of chronic lithium on the elevation of brain glucose metabolism and on dopamine D2 receptor-initiated signalling, via effects on AA turnover in the brain.[78, 79] In addition to these findings, it has been shown that AA metabolism to eicosanoids in the brain is increased by a dietary deficiency of omega 3 PUFA. Rats fed an omega 3 PUFA deficient diet for 15 weeks showed, as expected, decreased DHA in the frontal cortex and alterations in expression of enzymes related to AA metabolism. Rao et al. showed that PLA_2, $iPLA_2$ and COX-1 expression decreased while $cPLA_2$, $sPLA_2$ and COX-2 expression increased.[80] There was also a decrease in the expression of BDNF, CREB and p38 mitogen-activated protein kinase (MAPK) activity.[81] Furthermore *in vitro* administration of DHA to astrocytes induced BDNF expression. This could be blocked by a p38 MAPK inhibitor leading to the conclusion that p38 MAPK is an important regulator of BDNF expression.[81] In contrast, dietary supplementation with omega 3 PUFA normalizes BDNF levels that are reduced with brain injury. As expected downstream signalling effectors, synapsin I and CREB, also decreased with brain insult and were restored by dietary omega-3 supplementation.[55]

An alternative theory to the cause of depression involves the possible decrease in membrane integrity. Reduction in the amount of DHA in a cell membrane will decrease membrane fluidity.[82,83] This may lead to abnormal cellular functions as changes in membrane fluidity may impair receptor activation and function, ion channel function, production of secondary messengers, enzyme activity, signal transmission, gene expression and secretion of neurotransmitters.

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AUTHOR DISCLOSURES

Daniella Tassoni, Gunveen Kaur, Richard S Weisinger and Andrew J Sinclair, no conflicts of interest.

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