N-3 polyunsaturated fatty acids in psychiatric diseases: Mechanisms and clinical data

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Abstract

The lipids constitute majority of dry weight of mature human brain. From lipids, 35% is comprised of PUFA with long chain (LC-PUFA), especially docosahexaenoic acid (DHA) of n-3 family and arachidonic acid (AA) of n-6 family. Humans are dependent on dietary intake of both AA and DHA. Interestingly, the dietary n-6/n-3 ratio increased considerably during last century. LC-PUFAs play numerous roles in the brain, including structural (forming the physico-chemical properties in the lipid bilayer of cellular membranes) and signaling ones. Moreover, they influence neurogenesis and neurotransmission within the nervous tissue. The metabolites of PUFA modulate immune and inflammatory processes in the brain, oxidative stress as well as its consequences. Of high importance is also their connection with several metabolic factors involved in the proper function of the brain and/or were discovered to play a role in the pathogenesis of neuropsychiatric diseases – melatonin, homocysteine, leptin, and adiponectin. This review gives short view of the metabolism and possible mechanisms of PUFA n-3 action in the brain, and their role in the pathogenesis of psychiatric diseases.

Abbreviations:
PUFA - polyunsaturated fatty acids
AA - arachidonic acid
DHA - docosahexaenoic acid
EPA - eicosapentaenoic acid
CNS - central nervous system
LC-PUFA - long-chain polyunsaturated fatty acids
TRP channels - transient receptor potential channels
GSH-Px - glutathione peroxidase
MARCKS - myristoylated alanine-rich C kinase substrate
VMAT2 - vesicular monoamine transporter 2
raf-1 - the acronym RAF is derived from Rapidly Accelerated Fibrosarcoma
k Ras - Kirsten RAt Sarcoma viral oncogene homolog
PI3-kinase - phosphatidylinositol-3 kinase
MMSE - Mini Mental State Examination
βFGF - Fibroblast growth factor-beta
IL - interleukin
MB-COMT - membrane-bound catechol-O-methyltransferase
Erk 1/2 - extracellular signal-regulated kinase-1/2
sorLA - sorting protein-related receptor
5-HIAA - 5-Hydroxyindoleacetic acid
RCT - randomized clinical trial
O&NS - oxidative and nitrosative stress
ME/CFS - myalgic encephalomyelitis/chronic fatigue syndrome
1. INTRODUCTION

In the last two centuries, the human nutrition has considerably changed in the sense of higher total energy intake. Moreover, dietary content of saturated fatty acids (SFA) has increased at the expense of polyunsaturated fatty acids (PUFA), especially those of n-3 family (Simopoulos 1999). These changes are thought to be related with significant increase of prevalence of obesity, type 2 diabetes mellitus and cardiovascular diseases (Reddy & Katan 2004; Simopoulos 2008). Furthermore, there is growing evidence that the pathogenesis of some neuropsychiatric disorders (depression, schizophrenia, Alzheimer disease) also involves (apart from genetic) the nutritional factors, such as the fat intake, the content of PUFA n-3 and their ratio to PUFA n-6 (Young & Conquer 2005).

2. POLYUNSATURATED FATTY ACIDS – OVERVIEW AND METABOLISM

Fatty acids (FA) are higher monocarboxylic acids, most of them with even number of carbons in the molecule. According to the number of double bonds in hydrocarbon chain, FA are traditionally divided into saturated FA (SFA, without double bond), monounsaturated FA (MFA, one double bond), and PUFA (with two and more double bonds). The principal metabolic pathways for changes in FA chain are presented on Figures 1a and 1b.

In humans, the PUFA n-3 and n-6 bound in lipids form an integral part of biological membranes. These acids modulate membrane fluidity, the interactions between lipid and protein part and also modulate the function of various enzymes, transporters as well as membrane receptors (Murphy 1990). The PUFA can change the cellular response on the extracellular signals with acylation of intracellular proteins (Pike 2004), they are also structural parts of second messengers, such as diacylglycerol (DAG), the functions of which they can influence in this way (Hichami et al. 2005). The last, but not the least, issue is the possible action of PUFA on the transcription of many genes (Deckelbaum et al. 2006). The enzymatic oxidation of twenty-carbon PUFA [dihomo-gammalinolenic (DGLA), 20:3n-6; arachidonic (AA), 20:4n-6; eicosapentaenoic (EPA), 20:5n-3] (Fitzpatrick & Soberman 2001) gives rise to the eicosanoids, the compounds with many important biological effects. Other oxidative metabolites of PUFA include resolvins (resolution-phase interaction products) with immunoregulatory and antiinflammatory effects, which are synthesized from EPA and DHA: series E resolvins (RvE) and D (RvD), and (neuro)protectins from DHA in glial cells of CNS; these derivatives downregulate the expression of inflammatory cytokines (see Serhan et al. 2011 for review).

3. PUFA IN CENTRAL NERVOUS SYSTEM

3.1 PUFA content in brain and the relation to other body compartments

The lipids constitute 50–60% of dry weight of mature human brain. From these, 35% is comprised of PUFA with long chain (LC-PUFA), especially AA and DHA. The analyses of FA profile in the fat from frontal cortex revealed that the PUFA n-6 content reached 17% (mainly AA) and the content of PUFA n-3 was as much as 14% (only DHA, other PUFA n-3 – EPA, ALA and 22:5n-3 represented less than 1%) (McNamara & Carlson 2006). The arachidonic acid can be found in all tissues, whereas DHA prevails in grey matter, retina and testes. Interestingly, the content of AA and DHA increases during the period of maximal brain growth, i.e. three months before delivery and for the short period of time in the postnatal life (Wainwright 2000). The postmortem analyses of FA content in brain tissues of individuals with neuropsychiatric diseases are not consistent. Many confounding factors can bias the results, such as undetected exposition to antidepressants, mood stabilizers, antipsychotics, long-time alcohol abuse, or the fat content/quality (McNamara & Jandacek 2011). The high dietary intake of LCPUFA n-3 was selectively associated with higher volume of gray matter in the region taking part in corticolimbic circuitry (subgenual anterior cingulate cortex, right hippocampus and right amygdala), the dysfunction of which represents pathologic marker of mood disorders such as depression (Conklin et al. 2007). The dietary intake of EPA and DHA correlates with their raised concentrations in plasma as well as erythrocyte phospholipids and it also correlates with decreased content of AA (Arterburn et al. 2006). Carver et al. analyzed FA content in the samples of brain cortex of 58 individuals aged 2–82 years; the authors found statistically significant correlations between AA as well as DHA content in erythrocytes and brain cortex in samples of those older than 18 years (Carver et al. 2001).

3.2 The effects of PUFA in CNS

PUFA were found to exhibit their effects in CNS through various mechanisms connected with (i) characteristics of neuronal membranes, (ii) intracellular signalization, gene expression and transcription, (iii) modulation of immune and inflammatory processes, (iv) effects on neurogenesis, (v) neurotransmission, especially of serotonin and dopamine type, (vi) crosstalk with metabolic factors functioning in CNS.

3.2.1. Physical-chemical characteristics of neuronal membranes

PUFA considerably influence the physical-chemical characteristics of membranes and consequently the function of the structures connected with membranes (ion channels, receptors, cellular transporters etc.) (Murphy 1990; Mourek et al. 2009). The increased membrane fluidity enhances lateral movements of
proteins within the lipid bilayer and enables easier interactions between the proteins located in the membrane. Sufficient content of DHA in phospholipids of retinal rods supports the activation of rhodopsin and the conformational changes leading to the transformation into the active form, metarhodopsin II (Stinson et al. 1991). Rhodopsin, which belongs to the G-protein coupled receptors (GPCR), is responsible for night vision. DHA increases the activity of Na\(^+\)/K\(^+\)-ATPase, which is located in the neuronal membranes and keeps the resting membrane potential (Gerbi et al. 1998). On the contrary, DHA inhibits Ca\(^2+\)-ATPase (Kearns & Haag 2002). DHA accumulates in neuronal synaptic membranes mostly in phosphatidylethanolamines (PE) and phosphatidylserines (PS). The decreased content of DHA in PS due to DHA deficiency conduces to low vision.

**Fig. 1a** 1b. Docosahexaenoic acid (DHA, 22:6n-3) is fatty acid of n-3 family with 22 carbon atoms in the chain and 6 double bonds. The n-3 stands for the position of the first double bond from the methyl end of the chain, i.e. the bond is located between the third and the fourth carbons. The humans can synthesize SFA and MUFA (see next Figure), but they cannot introduce the double bond nearer than to the ninth carbon to the carboxyl end (D9 desaturase). Therefore, humans are not able to biosynthesize double bonds on the positions n-3 and n-6. The linoleic (18:2n-6) and α-linolenic (18:3n-3) acids, which are the precursors of respective PUFA families, must be ingested in the diet and are referred to as essential FA (EFA).
expression of membrane protein MARCKS (myristoylated alanine-rich C kinase substrate) and disturbed homeostasis of intracellular calcium (McNamara & Carlson 2006). PUFA n-3 can modulate either directly or indirectly the function of TRP channels (transient receptor potential channels), which take part in neurotransmitter release, redox signalization and modulation of Ca^{2+} level in mitochondria (Leonelli et al. 2011). The changes in function of the abovementioned channel proteins could participate in the pathogenesis of neurodegenerative and psychiatric diseases (Chahl 2011).

3.2.2. Intra- and intercellular signalization, gene expression and transcription

The membrane phospholipids are potential source of signaling molecules with both intra- and extra-cellular mode of action. The phospholipase A2 liberates AA, EPA and DHA from molecules of PL. These acids are metabolized with cyclooxygenases, lipoxygenases or cytochrome P450 monoxygenases transforming the respective FA into eicosanoids (AA and EPA) or docosanoids (DHA) (See Figure 2). Eicosanoids and docosanoids easily diffuse through neuronal membranes and can act as autocrine or paracrine signaling molecules. The PUFA molecules themselves can be intracellular second messengers or their content in signaling structures influences the function of transcriptional factors and gene expression (Deckelbaum et al. 2006). For example, DHA released from membrane with iPLA2 (calcium-independent phospholipase A2) takes part in the modulation of signal transduction or as a part of the diacylglycerol (DAG) molecule, and DHA enhances DAG-dependent activation of protein kinase C. DHA can also be transformed into docosanoids that have antiinflammatory effects and protect neurons from oxidative damage (Bazan 2009, Shimazawa et al. 2009). PUFA n-3 influence the gene expression not only in liver and adipose tissue (Deckelbaum et al. 2006), but also in brain. These genes govern synaptic plasticity, signal transduction, the interactions of cytoskeleton with cellular membrane, the formation of ion channels, regulatory proteins and other factors (expression of synuclein α and γ, calmodulins, actin, ras oncogenes and other) (Kitajka et al. 2002).

**Fig. 2.** Production of oxylipins from polyunsaturated fatty acids.
3.2.3. Modulation of inflammation and oxidative stress
The twenty-carbon derivatives of AA, EPA and DGLA play an important role in the human metabolism (Fitzpatrick & Soberman 2001). In general, the metabolites derived from AA are proinflammatory, whereas the EPA and DHA derivatives are antiinflammatory (see Figure 2). In membrane PL, AA is bound preferentially in PE, phosphatidylcholine and phosphatidylinositol. Arachidonic acid and its metabolites are involved in synaptic signalization, neurotransmitter release; they also influence brain perfusion and expression of neuronal genes (Bosetti 2007). The disturbed metabolism of AA in brain was related to many neurodegenerative and psychiatric diseases, such as (e.g.) Alzheimer disease, and depressive disorders (Bazan et al. 2002, Sublette et al. 2004). The inflammatory cytokines (IL-1β, IL-2, IL-6, interferon-γ and TNFa), activate hypothalamo-hypophysary axis, decrease the concentrations of neurotransmitter precursors and further change their metabolism (Maes & Smith 1998). The AA molecules, released from PL in cellular membranes, are transformed by cyclooxygenases (COX), which are also referred to as prostaglandin H syntheses (PGHS). PGHS produces PGH₂, the precursor for prostanooids, which are compounds with high tissue specificity. In brain, PGH₂ is a precursor for PGE₂ (Bosetti 2007). EPA can inhibit the production of eicosanoids from AA by direct inhibition of COX. Moreover, EPA and DGLA compete with AA for many eicosanoid forming enzymes, which further underlines their antiinflammatory effects. Arachidonic acid stimulates the biosynthesis of glutamate, the excess of which potentiates the neuronal destruction resulting from the overproduction of oxygen radicals. On the contrary, DHA increases the level of serotonin and acetylcholine (Minami et al. 1997, Vancassel et al. 2008, Mc Namara et al. 2010) and may act as an antioxidant (Shimazava et al. 2009).

3.2.4. Neurotransmission
Both the inter- and intra-cellular signal transduction is influenced by the concentration of neurotransmitters, their storage in vesicles and the function of presynaptic and postsynaptic receptors. The pathophysiology of neuropsychiatric diseases involves mainly neurotransmitters of catecholamine type (dopamine, noradrenaline, and serotonin), amino acids (glutamate, γ-aminobutyric acid) or acetylcholine. The animal models give us some insight into the interaction between the content of PUFA n-3 and neurotransmitters. The PUFA n-3 deficient rats had by 40–60% lower content of dopamine in frontal cortex (Delion et al. 1994), and lower content of dopamine in synaptic vesicles, higher expression of D2 receptors and lower content of vesicular monoamine transporter 2 (VMAT2) in nucleus accumbens (NAC), whereas the number of D2 receptors decreased in frontal cortex (Zimmer et al. 2002). NAC belongs to mesolimbic dopaminergic system that plays a role in cognitive and affective functions. The animals deficient in PUFA n-3 exhibit dysbalance between dopaminergic pathways, which is shifted to mesolimbic one. This dysbalance can participate in observed changes in attention, motivation and emotion motivation, reward answer and learning skills (Chalon 2006).

3.2.5. Neurogenesis and neuronal survival
Many studies proved the significance of PUFA n-3 (especially DHA) for the proper brain development in children; the importance for adult brain is currently under discussion. The experimentally induced lower intake of PUFA n-3 led to substantial decrease of DHA content in neurons, which was accompanied with higher content of PUFA n-6. In the nervous tissue, DHA is abundant in phospholipids, such as PE and PS. Higher intake of DHA causes increased synthesis of PS that is involved in cellular signalization. Elevated content of PS leads to enhanced translocation of raf-1 and PI₃ kinases to plasma membrane, increased activity of PI₃ kinase, which consequently diminishes the activation of caspase-3 and inhibits apoptosis (Marszałek and Lodish 2005). Interestingly, in some other cell types DHA can trigger apoptosis, as was shown for CaCo-2 colon cancer cell lines (Narayanan et al. 2001).

PUFA n-3 can favorably influence neoneurogenesis. The changes in the content (and the fluidity) of the neuronal membrane bring about the changes in quaternary structure of membrane proteins, including transporters and receptors (Bourre et al. 1991). The membrane fluidity influences the serotonin binding to the membranes and, secondarily, also the neurogenesis. The positive influence of PUFA n-3 is exerted via their effect on inflammatory cytokines (decreased concentrations of IL-1β and TNFα) (Shahbakti et al. 2004). The activation of microglial cells during chronic inflammation disrupts the neurogenic processes in hippocampus, whereas the inhibition of inflammation by tetracycline restores the neurogenesis in experimental rats (Ekdahl et al. 2003). Another possible mechanism, by which PUFA n-3 favorably influence the brain neurogenesis, includes higher expression of brain-derived neurotrophic factor (BDNF) (Cysneiros et al. 2010).

3.2.6. Metabolic pathways in CNS
3.2.6.1. Homocysteine (Hcy)
Hyperhomocysteinemia (HHcy) is not only risk factor for atherosclerosis and thrombosis, but also higher levels of Hcy are connected with inborn defects of neuronal crest, autoimmune diseases, osteoporotic fractures and neuropsychiatric diseases. HHcy was observed in euthymic patients with bipolar disorders (Dittmann et al. 2007), schizophrenics (Henderson et al. 2006), and patients with depressive disorders (Folstein et al. 2007). The concentration of homocysteine (Hcy) is the result of the interaction between dietary and genetic factors; most of the mildly elevated levels of Hcy is caused by the deficiency in vitamins B, especially...
folate, B12 and B6 (pyridoxal phosphate), which are the cofactors of metabolic pathways keeping stable level of Hcy (Hankey & Eikelboom 1999). The concentration of Hcy can be decreased with administration of PUFA n-3 (Zeman et al. 2006); the underlying mechanism is probably connected with the expression of enzymes taking part in Hcy metabolism (Huang et al. 2012). The Hcy concentration negatively correlated with the content of DHA both in serum platelet PL (Li et al. 2007) and plasma PC (Zeman et al. 2006). HHcy in depressive patients was accompanied with low levels of folate and S-adenosylmethionine (SAM) in serum and cerebrospinal fluid, also with low 5-HIAA and homovanillic acid (Bottiglieri et al. 2000). On the contrary, the treatment with SAM had antidepressive effects (Miller 2008). In HHcy states, the enzymes catalyzing methylation of catecholamines are inhibited. The brains of the patients with Alzheimer disease and HHcy had lower activity of phenylethanolamine N-methyltransferase (PNMT) and catechol O-methyltransferase (COMT) (Kennedy et al. 2004).

Other possible connection between HHcy and psychiatric diseases is the relationship of HHcy with dysregulated methylation of DNA in the gene promoter regions. In the study by Abdomaleky et al. (2006), it was found that MB-COMT promoter DNA is often hypomethylated in schizophrenics as well as in the bipolar disorder patients, which leads to overexpression of MB-COMT and increased degradation of dopamine in the frontal lobe. The experiments carried out on rats proved that high levels of Hcy attenuate the neurogenesis in hippocampus via inhibition of FGF-dependent activation of Erk1/2 (Rabaneda et al. 2008). Ravaglia et al. (2003) described in healthy individuals independent and gradual association of high level of serum Hcy with cognitive disorder measured with MMSE. HHcy is also known to raise the content of β-amyloid due to overexpression of γ-secretase and phosphorylation of amyloid precursor protein in experimental animals (Zhang et al. 2009).

3.2.6.2 Melatonin

Melatonin, (N-acetyl-5-methoxytryptamine) is produced mainly in the pineal gland, but also in other tissues. In humans, it plays an important role in the regulation of circadian biorhythms. The production of melatonin is higher in the dark periods, whereas its production decreases in the daylight. The regulation of melatonin biosynthesis is influenced by hepoxilins (derivatives of PUFA n-3 and PUFA n-6). PUFA n-3 and PUFA n-6 probably regulate the formation of hepoxilins and melatonin in pineal gland (Catalá 2009). Melatonin acts as an effective scavenger of hydroxyl and peroxyl radicals and also induces the production of antioxidant enzymes, such as GSH-Px (Reiter et al. 2008). The antioxidative effects of melatonin could be of high importance for favorable influence on neurodegenerative and psychiatric diseases (Alzheimer disease, schizophrenia, affective disorders), in the pathogenesis of which the oxidative stress is highly involved (Kodyrková et al. 2009; Maes 2011a; Anderson et al. 2012). One study found neuroprotective effect of melatonin administration in the model of hypoxic-ischemic encephalopathy in rats (Signorini et al. 2009). However, the studies examining the antidepressive effect of melatonin gave contradictory results. One derivative of melatonin, agomelatonin, has been reported to be an effective antidepressant therapy (Fornaro et al. 2010).

3.2.6.3 Leptin and adiponectin

Brain leptin significantly influences neurogenesis, axon growth and synapsis formation in the hypothalamus, hippocampus and other brain regions including the cortex (Paz-Filho et al. 2010). Furthermore, the interaction between leptin and serotonergic system was proved (Charnay et al. 2000). Leptin modulates various brain functions, e.g. the learning and memory skills. It is supposed that the dysregulation of leptin is involved in the pathogenesis of depression and Alzheimer disease; the leptin resistance cannot be excluded as well (Lu 2007). The mechanisms of action of adiponectin in brain have not been elucidated yet. Several studies described lower serum adiponectin in depressive disorder (Zeman et al. 2009), and the concentration of adiponectin negatively correlated with the stage of depression expressed as HAMD score (Zeman et al. 2009).

PUFA n-3 can modulate the levels of adipokines (including adiponectin and leptin) and consequently their effect in brain tissue. In the study by Peyron-Caso (Peyron-Caso et al. 2002), the administration of PUFA n-3 in insulin resistant rats increased leptin levels, other study (Rossi et al. 2005) found that PUFA n-3 counteracted the inhibition of secretion of leptin that was induced by long-time saccharose rich diet. However, another study did not find any effect of PUFA n-3 on leptin level (Flachs et al. 2006). Adiponectin levels are reported to be increased (Flachs et al. 2006; Rossi et al. 2005), but not always (Lorente-Cebrián et al. 2006) after the PUFA n-3 administration. The principal metabolic effects of PUFA n-3 include their apparent hypotriglyceridemic action (Harris et al. 1989; Žák et al. 1990). Hypertriglyceridemia leads to deteriorated transport of leptin through blood brain barrier (Banks et al. 2004), which can contribute to the peripheral leptin resistance.

3.2.7 Brain PUFA deficiency

The animal experiments showed that young individuals are more prone to EFA deficiency than the adults (Sardesai 1992). The western type of diet usually contains sufficient amounts of PUFA; therefore, the EFA deficiency in adults is limited to those being on total parenteral nutrition (TPN) (Richardson & Sgoutas 1975) that causes higher level of insulin, which slower the fat (EFA) mobilization from the adipose tissue depots (Sardesai 1992). The administration of fat-free TPN led after 3 months to alopecia, brittle nails, squa-
mous dermatitis and increased susceptibility to infections (Richardson & Sgoutas 1975; Sardesai 1992). Deficiency of LCPUFA can also result from disturbed metabolic pathways transforming LA and ALA to more unsaturated PUFA n-6 and PUFA n-3 analogues (See Figure 1a). The deficiencies in D6 (Willard et al. 2001) and D5 (Moore et al. 1995) desaturases were described. The patients had signs of multineuronal degeneration and mental retardation. The indices of lacking D6 desaturase activity were also observed in patients with Sjögren-Larsson syndrome, genetic disorder with frequent progression to paraplegia and mental retardation (Hernell et al. 1982). Deficiency of n-6 and n-3 PUFA have different neurologic signs (Table 1).

The diet deficient in PUFA n-3 given to Rhesus monkeys and rats led to disturbed vision, abnormal electroretinogram and polydipsia. (Reisbick et al. 1990a; Reisbick et al. 1990b; Faldella et al. 1996). The EFA deficiency in humans is often connected with disturbed learning and behavioral skills (Stevens et al. 1996; Maes et al. 1996); the signs and symptoms of this deficiency depend on the extent and general nutritional status [simultaneous carency of vitamins and/or minerals (Siguel 1994)]. Siguel and Lerman (1996) proposed the term EFA insufficiency for the patients, who exhibit in the plasma FA profile the same type of abnormalities as the patients with EFA deficiency (high conversion of n-3, n-6 and n-9 FA to respective derivatives and accumulation of MUFA).

4. PUFA IN SELECTED PSYCHIATRIC DISEASES

4.1 Schizophrenia

The patients with schizophrenia have abnormal metabolism of PL, more specifically, lower concentrations of PS, PC and PE in cellular membranes as a consequence of PUFA (AA, EPA, and DHA) deficiency. The deficiency was proved in erythrocyte membranes and in post mortem brain specimens (Horrobin et al. 1991, Peet et al. 2004). The membrane PL are important for signal transduction via neurotransmitters, which is mediated by neuronal receptors; therefore, their abnormal metabolism is sometimes linked with the disturbed information handling in schizophrenics (Mahadik & Evans 2003). Some authors (Fukuzako et al. 1999; Keshavan et al. 2000), but not all (Puri et al. 2008), found using $^{31}$P magnetic resonance spectroscopy (MRS) low concentrations of phosphomonooesters and higher levels of phosphodiesters in temporal and frontal lobes in schizophrenic brains. This could point at higher intensity of PL metabolism and further corresponds with high concentrations of Ca$^{++}$ independent PLA$_2$, the enzyme cleaving the FA from sn-2 position of PL, in blood and brains of schizophrenics (Ross et al. 1999). The decreased content of PUFA can result from higher oxidative stress or improper nutritional habits in schizophrenia. The arachidonic acid, after being released from PL molecule, can be metabolized into many metabolites, some of them interfering with the homeostasis of neurotransmitters, PI signalization cascade and neuromodulation by endocannabinoids (Yao & van Kammen 2004). Recently, the conceptualization has been introduced that schizophrenia similarly as depression (see below in paragraph 4.2.1.) can be viewed as a condition, in which the dysregulation of the immune system, oxidative and nitrosative stress (O&NS) as well as the tryptophan catabolite pathway play a role (Anderson et al. 2012). This novel concept, the neuroprogression, links neuroanatomical dysfunctions, lowered neurotrophic factors as well as a neurocognitive decline. The frame includes a possible role of PUFA n-3 being a part of the antioxidant system, which was used both in preventive and adjuvant therapy of schizophrenia (Pandya et al. 2012).

There were conducted many placebo-controlled studies which aimed at PUFA n-3 supplementation to the schizophrenic patients. However, the results are inconsistent, often comparable to the placebo group (Ross et al. 2007). In RCT lasting for 12 weeks and enrolling 76 individuals with subthreshold psychosis aged 13–25 years, the supplementation with PUFA n-3 (1.2 g/day) decreased the cumulative risk for the progression into manifesting psychosis by 22.6 % ($p=0.007$) (Ammringer et al. 2010).

4.2 Affective disorders

4.2.1. Depression

Major depression

It is now becoming evident that in major depression, progressive neuropsychopathological processes are involved. Neuroprogression is a phase associated and potentially deteriorating process including the combination of impaired neuroplasticity, reduced neurogenesis coupled to increased apoptosis and neurodegeneration (Maes et al. 2012). The recurrent episodes of depression are connected with the decline of cognitive functions together with increased risk of Alzheimer disease. The probable factors involved include oxidative stress leading to modification of DNA and lipid peroxidation. The antidepressive treatment was shown to improve the parameters of oxidative stress (Maes et al. 2011b). Possible beneficial effects of PUFA n-3 in depression are

Tab. 1. Neurologic characteristics of n-6 and n-3 EFA deficiency.

<table>
<thead>
<tr>
<th>n-6</th>
<th>n-3</th>
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<tr>
<td>Clinical signs</td>
<td>growth retardation</td>
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<tr>
<td>Reproduction disorders</td>
<td>Abnormal electroretinogram</td>
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<tr>
<td>Polydipsia</td>
<td>Blurred vision</td>
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<tr>
<td>Polydipsia</td>
<td>Decreased sensitivity</td>
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in link with the conception of neuroprogressive theory of depression (Moylan et al. 2012), as PUFA n-3 have the antiapoptotic, anti-inflammatory and antioxidative effects in CNS (Pandey et al. 2012).

Epidemiological data show that the fish consumption negatively correlates with the prevalence of depression in various populations (Hibbeln 1998). Lower levels of PUFA n-3 are connected with higher incidence of depression (Tiemeier et al. 2003). The depressive patients have lower content of PUFA n-3 in PL of various tissues – erythrocytes (Edwards et al. 1998, Peet et al. 1998), serum (Maes et al. 1996; Maes et al. 1998), adipose tissue (Mamalakis et al. 2006), and brain (McNamara et al. 2007) probably as a consequence of increased oxidative stress. Moreover, the concentrations of PUFA n-3 negatively correlate with the severity of depressive symptomatology (Conklin et al. 2007; Feart et al. 2008; Tiemeier et al. 2003). The lower content of PUFA n-3 is often accompanied with higher values of AA/EPA and AA/DHA ratios and/or PUFA n-6/n-3 ratio (Adams et al. 1996, Frasure-Smith et al. 2004). Restricted intake of PUFA n-3 in animals increases the depression and aggression scores (DeMar et al. 2006). Concomitantly, it was observed that the central serotonergic and dopaminergic transduction decreased together with lower number of hippocampal neurons. The dietary supplementation of DHA to rats brings about higher content of brain noradrenaline, serotonin, and acetylcholine and promotes neurite growth in hippocampal neurons (Calderon & Kim 2004; De Mar Jr. et al. 2006). The studies on healthy volunteers taking high PUFA n-3 doses proved (with the help of structural MR) increased amounts of gray matter in brain regions important for emotive and cognitive functions – the right hippocampus, the right amygdale and anterior cingulum (Conklin et al. 2007).

Recently, a new metaanalysis on PUFA n-3 in the treatment of depression was published (Appleton et al. 2010). The metaanalysis supports the hypothesis about the beneficial therapeutic effects of PUFA n-3, but it states that the results are difficult to summarize and evaluate due to considerable heterogeneity. Pronounced effect of PUFA n-3 was found in the patients with more severe symptomatology, whereas in the individuals without diagnosed depressive disorder, the effects on mood were weaker. The heterogeneity of the published results is probably caused by many factors, such as variable content of PUFA n-3, n-6 in the diet, placebo composition, age, gender, the accessory treatment, duration of the study, the dosage and type of PUFA n-3, or in the way the depression is evaluated (Appleton et al. 2010).

4.2.2 Bipolar affective disorder

It is supposed that PUFA n-3 play a role also in the bipolar disorder. Stoll and coll. compared in bipolar disorder the effect of olive oil (active placebo) and fish oil (equaling daily dosages of EPA 6.2 g/day and DHA 3.4 g/day). In the group taking fish oil, the authors observed significant decrease in number of relapses of the disorder. PUFA n-3 improved the depressive, but not the manic signs of the disorder (Stoll et al. 1999). Similarly, Frangou et al. (2006) conducted double-blind, placebo controlled study in 74 patients with bipolar disorder. They found that 12-week administration of 1 or 2 g/day of EPA had significant effect on the depressive, but not manic symptoms, when both EPA groups were compared to the placebo group. PUFA n-3 were also tried as the treatment of bipolar disorder in children and adolescents. In juvenile bipolar disorder, the dosage of EPA+DHA only slightly alleviated manic symptoms (Wozniak et al. 2007). Recent metaanalysis including only randomized designs lasting ≥4 weeks found that adjunctive administration of PUFA n-3 significantly corrected depressive symptoms without an effect on manic ones (Sarris et al. 2011).

4.2.3 Postpartum depression

Postpartum depression is symptomatic depressive disorder with the same symptoms as major depressive disorder or depressive disorder in a part of bipolar affective disorder. The populations with higher fish consumption have higher concentrations of DHA in breast milk and lower incidence of postpartum depressive disorder, whereas low fish intake during pregnancy is connected with higher incidence of depression (Golding et al. 2009). The hypothesis about the deficiency of PUFA n-3 in women with postpartum depression was supported by some authors (De Vriese et al. 2003), but later study did not find lower PUFA n-3 (Browne et al. 2009). During pregnancy, the PUFA n-3 are transferred into the fetus (the biomagnification effect), thus the mother is under higher risk of PUFA n-3 deficiency (Holman et al. 1991). The supplementation of PUFA n-3 to pregnant women was proposed to prevent from this type of deficiency, but newly published metaanalysis (Jans et al. 2010), with 309 women supplemented with PUFA n-3 and 303 women on placebo, did not prove the beneficial effect of the supplementation.

4.3 Alzheimer’s disease

Epidemiological data indicate that the sufficient dietary intake of PUFA n-3 (DHA) is associated with a significant reduction in dementia risk (Johnson & Schaefer 2006). One prospective study found that the individuals with the upper quartile concentration of DHA in plasma PC had (in comparison with those in the lower quartile) during 9 year follow-up significantly lower risk for AD (Schaefer et al. 2006). The patients with sporadic form of AD have lower content of protein SorLA (LR11) and its mRNA. This protein decreases the cleavage of amyloid precursor protein (APP) by α- and β-secretases, henceforward the formation of β-amloid. The administration of DHA to transgenic mice caused higher production of LR11 in neurons and lower production of β-amyloid (Ma et al. 2007). The influence of PUFA n-3 on the oxidative stress and inflammation, both of which...
playing an important role in the pathogenesis of AD, can be a part of the beneficial effect of PUFA n-3 in the prevention of AD. DHA and its derivative, neuroprotectin D1, enhance antioxidant defense of neurons by induction of antioxidant enzymes (Hashimoto et al. 2002) and antiapoptotic proteins (Jicha and Markesbery 2010). Moreover, DHA attenuates the production of toxic oligomers A beta (Hashimoto et al. 2008), which damage the synapses. PUFA n-3 support the formation of BDNF (brain-derived neurotrophic factor), that is important for neurogenesis and synaptic neuronal plasticity, both being impaired in AD (Bousquet et al. 2009).

PUFA n-3 deficiency is involved in the progression of other dementias and neurodegenerative diseases (Kidd 2008). In vascular dementia, the antiatherogenic and antithrombogenic effects play a role. It is supposed that PUFA n-3 act through their antiinflammatory and neuroprotective properties, as well as the ability to decrease the toxicity of α-synuclein (degenerative neuronal protein). Other protective effects include higher production of endogenous cannabinoids, the specific class of PUFA metabolites. Endogenous cannabinoids modulate dopaminergic activity in basal ganglia (Fernández-Ruiz et al. 2010).

Supplementation of PUFA n-3 to the patients with AD improves cognitive performance probably only in the subgroup with mild cognitive dysfunction (equaling to so-called amnestic form of mild disorder in cognitive functions, usually considered as a preclinical form of AD) (Freund-Levi et al. 2008). The reduction of risk for the development of AD was described in several studies (Barberger-Gateau et al. 2007). It seems that apoE is involved, because the beneficial effects of PUFA n-3 were not observed in the carriers of the e4 allele (Barberger-Gateau et al. 2007).

4.4 Other psychiatric diseases

4.4.1 Attention deficit hyperactivity disorder (ADHD)

Attention deficit hyperactivity disorder is very common disorder with onset in childhood, which inflicts 5–7% of children on average; the disorder often fades away, but in many cases, it persists to adolescent age and in 40–60% cases, it is still diagnosed in adults. Prevalence of ADHD in adults reaches 3–5% (Drtílková & Theiner 2008). About one quarter of ADHD patients suffers also from learning disorders, especially from reading and writing ones (Doggett 2004). It is supposed that the etiopathogenesis of ADHD includes both genetic and extrinsic factors. Both dopaminergic and noradrenergic dysfunctions were described – decreased transmission in the mesolimbic and frontal cortex areas. Some signs of ADHD can be accentuated with the PUFA deficiency, which often results from improper dietary habits (Antalis et al. 2006). Colter et al. (2008) found in adolescents with ADHD higher energy intake in comparison with the control group, but there was no difference in PUFA n-3 and n-6 intake; in the erythrocyte PL, the ADHD group had lower content of DHA, PUFA n-3 and lower PUFA n-3/n-6 ratio. These changes correlated with severity of ADHD symptoms evaluated with the Conner scale (Colter et al. 2008). Sorgi and coll. treated the children with ADHD, for 8 weeks with high dose of EPA + DHA (16.2 g/day from the beginning, in the 4th week, the dosage was titrated to reach the AA/EPA ratio in plasma PL similar to Japanese population). The observed findings included improved behavior of the patients and significant positive correlation between the decrease in AA/EPA ratio and global decrease in burden of disorder (Sorgi et al. 2007). In the new metaanalysis of the studies, it was found that the supplementation with PUFA n-3, especially with high doses of EPA, is modestly effective in the treatment of ADHD (Bloch & Quawasmi 2011).

4.4.2 Chronic fatigue syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), medical disorder or group of disorders (Sanders 2008), characterized by persistent fatigue accompanied by at least four of the following symptoms: substantial impairment in short – term memory or concentration; sore throat; tender cervical and axillary lymph nodes; muscle pain; multi – joint pain without selling or redness; headache of new type; unrefreshing sleep; and post exertion malaise lasting more than 24 hours for a minimum of six months in adults. Inflammation and oxidative and nitrosative pathways and a lowered antioxidant status are important pathophysiological mechanisms underpinning ME/CFS (Maes et al. 2009). Chronic fatigue syndrome shows a high degree of comorbidity with depression; many CFS patients develop depression during their illness, while fatigue is one of the key symptoms of major depression (Maes 2005). Some studies reported finding reduced levels of PUFA n-6 or PUFA n-3 in cell membranes or serum in patients diagnosed with CFS (Liu et al. 2003), while Warren (Warren et al. 1999) did not find any differences in red blood cell membrane lipids. Treatment of patients with CFS solely with a high-EPA containing supplement led to an improvement in their symptomatology within eight to 12 weeks (Puri et al. 2004).

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