

Psychoneuroimmunological Approach Regarding the Effects of Dietary Polyunsaturated Fatty Acid Content

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SSUMMARY: Psychoneuroimmunology is a challenging approach in biomedical sciences. It combines the field of psychology, neuroscience, neurology, genetics, biology, endocrinology and immunology. The increasing knowledge in the field of neuroscience, together with better research tools and techniques, enables the possibility to comprehend the true nature and etiology of processes that lead to modern epidemic of depression, obesity, hormonal dysfunction etc. With the outspread of Western diet the general population lacks adequate daily omega-3 fatty acid intake to satisfy the favorable ratio to other polyunsaturated fatty acids, such as omega-6. The disproportion of certain food components because of unfavorable dietary habits together with maladaptive reactions to stressors results in a state of overstrained homeostatic mechanisms- allostasis. In the case of persistent stressors this allostasis can't cope with the intensity and a real illness occurs. By replenishing dietary intake of omega-3 and maintain a favorable omega-3 to omega-6 ratio, a significant step would be made in terms of lowering inflammation and supporting the processes of healing.

KEYWORDS: Psychoneuroimmunology, Omega-3, PUFA, stress, HPA axis, DHA, Western diet

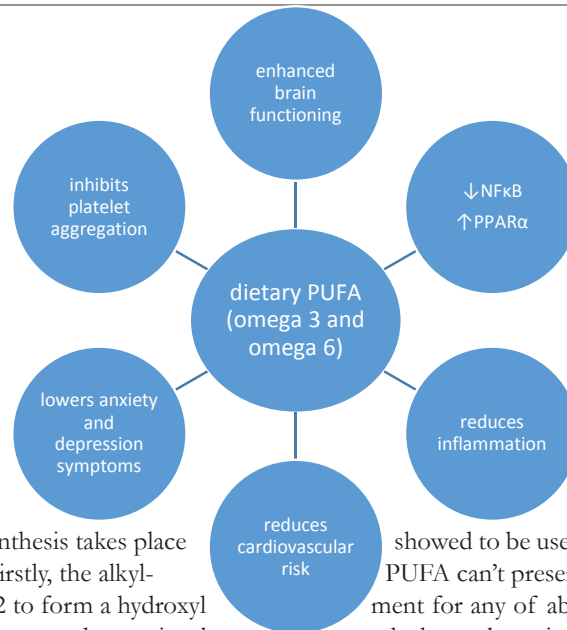
Psychoneuroimmunology (PNI), represents an integrative approach in tackling and understanding various human diseases and disorders, especially the ones carrying the prefixes 'autoimmune', 'idiopathic' or 'psychosomatic'. The areas of research focus on the existing connection between the mind and the body, mainly through the central nervous system (CNS) and autonomic nervous system (ANS). With the development of neuroimaging techniques in recent decades, it is now possible to non-invasively visualize the human brain and measure its activity in different states, including non-primary illnesses of the CNS according to clinical classification. Moreover, this approach focuses on elucidating and confirming the role of neural component in diseases which manifest as somatic and are treated symptomatically, while remaining oblivious to the etiology. Thus, understanding the true nature and cause of the symptoms will ultimately lead to a path for correcting the imbalance of the internal milieu. The intersection point for the mind (psycho), CNS or ANS (neuro) and immunological component is the brain. Through the prefrontal cortex, limbic system and ultimately the hypothalamus-pituitary-adrenal (HPA) axis, the brain represents an integrative center for neural, hormonal and immunological communication and response.¹ A disruption in any of the components leads to adaptive mechanisms which either overcome the noxious stimuli or succumb to a state of prolonged inflammation that ultimately results in a psychiatric or somatic condition.

Polyunsaturated fatty acids (PUFA) receive much attention in the recent years due to the observed connection between the Western diet and an arising epidemic of metabolic disorders in the general population.² It has been shown that the Western diet contains much less omega-3 fatty acids and a lot more omega-6. It is estimated that the ratio omega-3 to omega-6 used to be 1:1 in the hunter/gatherer era of humankind and in the Western diet it is closer to 1:50 in favor of omega-6.³ Both

omega-3 and omega-6 represent essential fatty acids and neither can be chosen as a strictly negative or strictly positive one. The balance of the ratio is what is important and by keeping it closer to one to one, metabolic syndrome incidence might be halted.⁴ The ratio of PUFA is not only important in somatic, but also in psychiatric conditions such as depression and dementia.^{5,6} Both mark a constant rise in incidence and both are linked to neuroinflammatory state in the brain.^{7,8,9,10} By daily consumption of the food that belongs to the Western type diet, a state of chronic low grade inflammation is achieved. If other negative habits such as smoking, sedentary lifestyle and immoderate alcohol consumption are also present in an individual, the pathophysiological mechanisms are amplified and the state of homeostasis is seriously compromised. An allostasis is achieved, a state of homeostasis with marked usage of coping mechanisms which ultimately puts an individual in a less favorable state to counter noxious stimuli.

Effects of dietary PUFA

Plasmalogens are ether phospholipids. Ethanolamine, choline and serine are the most notable polar head group. They also contain a vinyl-ether bond at the sn-1 position and an ester bond at the sn-2 position. This particular sn-2 position can be occupied by different fatty acids, including PUFA. The synthesis occurs in peroxisomes and endoplasmic reticulum. The starting molecule is dihydroxyacetone phosphate and its glycerol component as a main central part. In the first step of synthesis, an ester is formed with a fatty acid catalyzed by the enzyme dihydroxyacetone phosphate acyltransferase (DHAPAT). The fatty acid ester is then exchanged for a fatty alcohol and thus forming an ether-bond at the sn-1 position. The enzyme needed for this reaction is alkyl dihydroxyacetone phosphate synthase (alkyl-DHAP synthase). Both of these enzymes are found in



peroxisomes. The next part of the synthesis takes place in the endoplasmic reticulum (ER). Firstly, the alkyl-DHAP is reduced at the position sn-2 to form a hydroxyl group. Secondly, a fatty acid forms an ester at the previously prepared sn-2 position by the action of alkyl/acyl-glycerophosphate (GPA) acyltransferase. This position is important for integrating PUFA into the structure of plasmalogen. Thirdly, a polar head group such as ethanolamine or choline is added at the phosphate part of the molecule. The final step is the dehydrogenation process at the alkyl group bound on sn-1 and a vinyl ether is formed. The plasmalogen molecule is now complete.

The dietary intake of PUFA will dictate the availability of omega-3 or omega-6 to be present for the synthesis of plasmalogens and ultimately for incorporation in the cell membranes. Plasmalogens constitute 15-20% of total phospholipids in the cell membrane, especially in the brain (22%), heart (25%), kidney (20%) and skeletal muscle (20%). Certain areas of the brain contain more than 80% phospholipids in the membrane made from plasmalogens.¹¹ Delivering of the specific PUFA type as a plasmalogen results in different local effect. Linoleic acid (LA), arachidonic acid (AA) and dihomo- γ -linolenic acid (DGLA) belong to omega-6 fatty acids and linolenic acid, docosahexaenoic (DHA) and eicosapentaenoic (EPA) belong to omega-3 fatty acids. The metabolic products of DGLA, DHA and EPA produce generally favorable and anti-inflammatory effects (e.g. neuroprotectins, resolvins), while on the other hand AA is a precursor for mostly inflammatory metabolites. PUFA are not to be divided on good and bad, the ratio between them is important. In the countries where the Western diet prevails, there is a chronic deficiency of omega-3 fatty acids resulting in an unbalanced cell membrane composition and contributing to the state of chronic low grade inflammation.¹² DHA shows direct positive effect on neuronal health in forms of preserving LTP synaptic transmission¹³ and hippocampal growth in mice.¹⁴ Taking supplements that contain omega-3 fatty acids shows positive effects regarding symptoms of depression and cognitive impairment.^{15, 16, 17} However the studies were carried out in hundreds rather than thousands of examinees and further large-scale research are needed to yield stronger evidence. There is also an interest in the field of neurodevelopment for the effects of omega-3 and the importance of PUFA in regular and healthy neural growth. The mere percentage of plasmalogens present in the CNS and actual researches carried out show a great importance of PUFA for processes like myelination and Schwann cell differentiation.¹⁸ Daily omega-3 intake reduced anxiety symptoms in a study conducted in student population during exams¹⁹ and another randomized controlled trial

showed to be useful in treating depressive symptoms.²⁰ PUFA can't presently be recommended as a single treatment for any of above mentioned disorders, but current research show a boosting effect on health when used as a food supplement. The entire mechanisms aren't clear yet but some of them are known; activating PPAR- α and promoting transcription²¹, activating PPAR- γ ²², directly activating ion-channels.²³ One of the discoveries, regarding DHA brain derivative, is also worth mentioning. Synaptamide, or docosahexaenoyl ethanolamide, represents a structural analog of the endogenous cannabinoid – anandamide. It stimulates synaptogenesis and neurite growth in hippocampus.²⁴

Psychoneuroimmunology and PUFA connection

Since PUFA have an undoubtedly important function in preserving general homeostasis, but are also very much implied as a factor in proper brain functioning, it shouldn't be incredibly hard to grasp the interconnection between the PNI as a concept and the importance of PUFA when approaching a certain psychiatric or somatic disorder and its pathophysiology. A common underlying cause of most main diseases affecting the modern man is a deficient or dysfunctional immunological system. A significant prevalence of autoimmune, malignant, idiopathic or functional disorders is present. If the PNI approach is applied, it all starts with the mind, i.e. brain functioning.

Firstly, a noxious stimulus must be present. It can be generated from the environment (natural disaster, accident, work related stress, childhood trauma) or self-generated as a consequence of having bad or inadequate coping skills. The person ends up dwelling on negative thought over and over again. The repeating process translates to a dysfunction at the highest cortical levels and proceeds to lower – limbic, until finally reaching the HPA axis and thus affecting the entire body. Daily cortisol levels could serve as a significant marker in psychiatric disorders²⁵, but also in patients who suffer from a metabolic²⁶ or cardiovascular²⁷ illness. A state of permanent alarm overflows the body and homeostatic mechanisms begin to fulfill their role acutely until they become chronically purposeful, even self-damaging. The autonomic system shifts the entire body in sympathetic pathway, glucocorticoid secretion is elevated and the normal HPA axis is broken, diurnal rhythm is compromised, immunological system is overreacting, the liver shifts its metabolism to acute inflammatory pattern, endocrine glands functioning and hormone levels are disrupted.²⁸ The symptoms that are developed in an affected individual reflect the underlying pathophysiological processes present. This allostatic state perfectly sets up the body for

Table.1 Physiological and somatic consequences of chronic stress²⁸

Stimulation/ Up regulation	Inhibition/ Down regulation
CNS	
Hippocampus (HPA feedback loop dysregulation)	Leptin axis
Amygdala	Somatotropin axis
Mesolimbic-cortical	Gonadotropin axis
	HPA axis
HYPERTENSION	
Vasoconstriction mechanisms	Vasodilation mechanisms
-sympathetic tone (RAAS)	
-vasopressin	
-endothelin	
VISCERAL FAT/ METABOLIC SYNDROME	
Insulin resistance	Peripheral utilization of glucose
-Gluconeogenesis	Glucose tolerance
-Hyperinsulinemia	HDL-cholesterol
-Fat cell growth	Thrombolytic processes
LDL-cholesterol, FFA	
Coagulation processes	
OTHER	
Atherosclerosis	Osteoblast activity
Cardiovascular risk	TH1 response
Osteopenia/Osteoporosis	
Immune insufficiency	
IL-4, TH2 response	

developing metabolic syndrome and other endocrine disorders (e.g. eutyroid sick syndrome²⁹) or autoimmune reactions which also produce atopic and allergic reactions, dermatological conditions³⁰ and other organ dysfunctions. Once in an ill state, an individual exhibits sickness-behavior which shows that the brain is also affected by the inflammatory response pattern present in the periphery. The brain isn't considered to be such an immunologically privileged organ as it once was.^{31, 32} The entire process can start in the mind/brain as a maladaptive response to stressor and induce an inflammatory response in the periphery, just to return back to the brain as a neuroinflammation. A vicious cycle is formed! Where do PUFA come here? As the currently confirmed and observed pleiotropic effects of dietary PUFA show, with their application a proportion of the inflammatory state could be reduced and more importantly, have a protective effect on the brain itself – the central organ.³³ Reduction of the inflammatory state makes way for other techniques. In order to start with managing stress-related disorders, it would sound

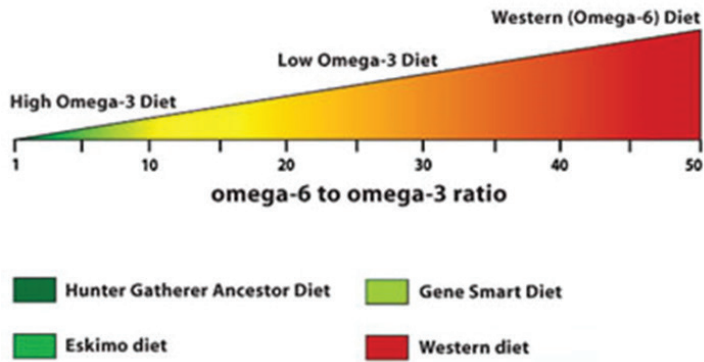
prudent to have an as-close-as-you-can healthy situation in the organ you need the most. The rise in, e.g. depressive disorder follows the technological development and lifestyle changes that come with it.³⁴ Obesity and diabetes type 2 are mostly lifestyle consequences, but from the PNI perspective it should be addressed as a mind/brain and peripheral organs dysfunction, thus the therapeutic approach should be integrative.

Conclusion

PNI is surely a promising field due to development of neuroscience and with increasingly available techniques for research, namely the neuroimaging techniques and easily made blood test. This concept might enable medicine, as an interdisciplinary profession it has become, to extend the knowledge even further and finally figure out what lies behind the prefix 'idiopathic'. PUFA deficiency is a result of spreading the Western diet among the globalized world and consequently the countries mark an increase in metabolic, cardiovascular and malignant diseases, but even more prominently in psychiatric disorders, e.g. depression (second leading morbidity by 2020!).³⁵ This all can not be attributed to mere aging of the population, because depression affects mostly middle-aged working people.³⁶ A common feature of metabolic and depressive disorder is that they put an individual at greater risk for developing concomitant diseases. Surely PUFA deficiency isn't the only brick in the wall, but by correcting the shortage of this nutrient in the body, a valuable resource is replenished.

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Fig 1. Omega 6 to Omega 3 ratio regarding diet³

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Psihoneuroimunološki pristup učincima unosa višestruko nezasićenih masnih kiselina u prehrani

SAŽETAK: Psihoneuroimunologija je izazovni pristup u biomedicinskoj znanosti. Stapaju se područja psihologije, neuroznanosti, neurologije, genetike, biologije, endokrinologije i imunologije. Rastuće znanje u području neuroznanosti, zajedno sa boljim istraživačkim metodama i alatima, omogućuje bolje razumijevanje etiologije procesa koji su doveli do modernih epidemija depresije, debljine i hormonalne disfunkcije. Raširenošću zapadnog tipa prehrane dnevno se ne unosi dovoljno omega-3 esencijalnih masnih kiselina u odnosu na omega-6. Nesrazmjer stanovitih komponenti u prehrani uz loše prilagodbene reakcije na stresore vodi u stanje prenapregnute homeostatskih mehanizama- u alostazu, stanje ravnoteže uz povećane metaboličke zahtjeve. U slučaju da stresor perzistira, alostaza ne može održati ravnotežu i manifestna bolest postaje prisutna. Zadovoljavajući dnevni unos omega-3 masnih kiselina i zadržavajući povoljan omjer za omega-6 masnim kiselinama, učinio bi se zanačajan korak u smanjivanju upale i podupiranju puta cijeljenja i ozdravljenja.

KLJUČNE RIJEČI: psihoneuroimunologija, omega-3, višestruko nezasićene masne kiseline, stress, osovina HHN, dokozaheksanoična kiselina, zapadni tip dijete

