Editorial

Can High w-6/w-3 Ratio of Fatty Acids in the Neuronal Cell Membrane Phospholipids Predispose Fear Behaviour?

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Polyunsaturated fatty acids (PUFAs) constitute key structural and functional components of phospholipid membranes in all body tissues including neuronal cell membranes [1-4]. They are highly concentrated in the central nervous system (CNS) including brain [1]. PUFAs have important role in nervous system activity, neuroplasticity of nerve membranes [2], synaptogenesis [3], synaptic transmission [4] and neurotransmitter uptake [1, 4, 5]. Most neurotransmitters; catecholamines, acetylcholines, cortisol, dopamine and serotonin, also influence the function of the other body systems, in addition to their effects on neuropsychiatric dysfunctions including emotional fear reaction [1, 5]. The biosynthesis of neurotransmitters has been shown to depend on a number of other essential nutrients such as tryptophan, tyrosine, arginine and choline that are also important in neuronal cell function. There is evidence that ω3 fatty acids and other nutrients can affect cognitive function, mood, type-A behaviour, anxiety and depression characterized with fear reaction [4-6]. It seems that the behaviour of fear is an emotional reaction that may be under control of amygdala and deficiency of w-3 fatty acids in the neuronal cell membranes of amygdala could be important in the electrophysiology of fear reaction.

In their landmark study [7, 8], the authors combined molecular genetics, anatomical, electrophysiological and behavioral approaches to identify a specific microcircuit in the brain. This finding appears to be one of the first neuron-level pathways for emotion ever identified. However, it could have been more interesting to find out biochemical abnormalities related to fatty acid content of neurons which are important in the pathobiology of neuropsychiatric dysfunctions [1-6, 9].There may be interesting implications of these results in the management of fear and anxiety, which are important manifestations of depression [1]. It is possible that targeting genetically identified population of neuronal cells with a drug could be more effective than general drug administration. The future targets of drug therapy would be to target specific cells in specific circuits by repairing specific deficit. Repair of w-3 deficiency in the specific circuits could be a most interesting approach because it is a normal content of the neurons. In one experiment, w-3 fatty acid and coenzyme Q10 deficiency has been observed in the ventromedial hypothalamus, hippocampus and other parts of the brain in streptzotocin induced diabetes in rats [9]. Treatment with w-3 fatty acids and coenzyme Q10 repaired the deficit causing significant decrease in oxidative stress and improvement in other parameters [9].

The role of various amygdala nuclei in processing Pavlovian conditioned fear has been studied extensively, but the function of heterogeneous neuronal subtypes within these nuclei remains poorly understood In one study, the authors used molecular genetic approaches to map the functional connectivity of a subpopulation of GABA-containing neurons, located in the lateral subdivision of the central amygdala, which express protein kinase C-δ [7, 8]. Channelrhodopsin-2-assisted circuit mapping in amygdala slices and cell-specific viral tracing indicate that protein kinase C-delta neurons inhibit output neurons in the medial central amygdala, and also make reciprocal inhibitory synapses with protein kinase C-delta$^-$ neurons in central amygdala. Electrical silencing of protein kinase C-delta neurons *in vivo* suggests that they correspond to physiologically identified units that are inhibited by the conditioned stimulus, called central amygdala units. This inhibitory microcircuit in central amygdala gates medial central amygdala output to control the level of conditioned freezing. There is no mention of neuronal cell membrane content of w-3 fatty acids, which are incorporated in the phospholipids of the neurons. It is possible that deficiency of w-3 fatty acids and excess of w-6 fatty acids in the neuronal cells of amygdala, particularly GABA-containing neurons, may influence electrical silencing of protein kinase C-delta leading to abnormal electrophysiological manifestations. Emotions and fear are also known to influence gut-liver and brain axis which may influence the release of leptin, cholecystokinin, PUFA-Coenzyme A and brain derived neurotrophic factor important in haemostasis.

Besides, an increased consumption of linoleic acid (C18:2ω6), saturated fat and trans-unsaturated fats, refined carbohydrates, may be pro-inflammatory leading to increased tissue levels of activating protein-1 (AP-1) and early growth response protein-1 (EGRP-1), which are transcription factors for pro-inflammatory cytokines [1-6]. These cytokines appear to be positively associated with mood, depression and type-A behaviour and also possibly with fear reaction particularly in patients with depression. Omega-6 fatty acids have adverse effects on all the proinfammatory cytokines as well as on neurotransmitters responsible for memory function, mood and behaviour [1-5]. The brain contains high concentrations of ω3 PUFAs and several studies suggest a role for ω3 PUFAs in neurotransmitter synthesis, degradation, release, reuptake and binding [4-6]. Fatty acids and phospholipids are part of all biological membranes. The membrane's fluidity, of crucial significance for its proper functioning, principally depends on its lipid components; PUFAs increase membrane fluidity according to their number of

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double bonds, whereas free cholesterol (CHL) increases membrane viscosity so that the end result depends on the PUFAs/CHL desaturation index. Docosahexaenoic acid deficit is mainly associated with dysfunctions of neuronal membrane stability and transmission of serotonin, norepinephrine and dopamine, probably being related to the aetiology of cognitive dysfunction, mood and ultimately depression. On the other hand, eicosapentaenoic acid is essential to balancing the immune function, genetic modulation and physical health as a consequence of reduction in the proportion of arachidonic acid (C20:4ω6) in cell membrane and prostaglandin E2 (PGE2) synthesis. We would gratefully appreciate the opinion of the readers of this journal on this aspect of neuronal dysfunction.

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