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Nutrient and the Mind-Body Axis, in Relation to Omega-3 Fatty Acids and Amino Acids

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Abstract: Noncommunicable Diseases (NCDs); obesity, type 2 diabetes mellitus, Cardiovascular Diseases (CVDs) and cancer have become major health problems in both developing and developed countries. Physical inactivity and increased intake of energy rich proinflammatory foods in association with genetic predisposition are common primary risk factors for these problems. Mind-body interactions and mechanisms in relation to hypothalamus neurotransmitters and vagus nerve have been discovered in causing NCDs. Apart from above risk factors. The role of salivary glands, liver and beta cells of pancreas and their interactions with hypothalamus and vagus nerve are important mechanisms to explain the neural and behavioural factors in the pathogenesis of NCDs. In this connection, the role of w-6/w-3 fatty acids ratio as well as essential and nonessential amino acids like glutamate, arginine and cysteine (the latter two being conditionally essential in some situations) and the sulphonic acid taurine have on brain function appears to be of great interest. This broad hypothesis focusses on the role of environment on mind-body connection in the pathogenesis of NCDs. Omega-3 fatty acids and amino acids possibly glutamate, can also improve neuronal efficiency causing improvement in taste, appetite, attention, cognitive performance and mood state. Omega-3 fatty acids can improve the electroencephalographic alpha and theta oscillations which are indicators of memory function. Treatment of NCDs; coronary atherosclerosis, hypertension and type 2 diabetes with an w-3 fatty acid rich Mediterranean diet may be protective, as it is also rich in amino acids. There is a need to study the role of amino acids, especially, glutamate in the pathogenesis of NCDs, because other 'amino' acids like arginine, taurine and cystiene have been found to be protective against cardiovascular diseases.

Key words: Noncommunicable Diseases (NCDs), Cardiovascular Diseases (CVDs), Anti-Tumor Necrosis Factor (TNF), Coronary Artery Disease (CAD)

INTRODUCTION

The diet of Homosapiens was characterized by natural foods; fruits, vegetables, green vegetables, seeds, eggs, fish, meat from running animals and honey (De Meester, 2009; Simopoulos and Meester, 2009; Singh *et al*., 2011; Eaton *et al*., 1988; 1998). These foods were also generally available to pre-agricultural humans which shaped modern human's genetic nutritional requirement. Cereal grains (refined) and vegetable oils that are rich in w-6 fatty acids and trans fats and low in amino acids are relatively recent addition to the human dietary patterns that represent dramatic departure from those foods and nutrients to which we are adapted (Table 1-3). Early man also had enormous physical activity without the same sustained level of mental stress of modern man. The role of fatty acids, essential and nonessential amino acids, antioxidants and vitamins in the prevention and pathogenesis of Noncommunicable Diseases (NCDs); Cardiovascular Diseases (CVD), type 2diabetes and insulin resistance are well known (Simopoulos and Meester, 2009; Singh *et al*., 2011). There is evidence that the Mediterranean diet which has similarity with Paleolithic diet can influence brain function related to

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taste and palatability and neuro-psychiatric disorders as well as mind-body connection (Eaton *et al*., 1988; 1998; Uneyama *et al*., 2008 McCabe and Rolls, 2007).

There have been marked changes in the human food supply with the development of agriculture about 10,000 years ago from now. However, only a no significant change in our genes has occurred during the past 10 century due to presence of w-3 fatty acids, amino acids, vitamins and antioxidants in the diet (Eaton *et al*., 1988; 1998). The spontaneous mutation rate for nuclear DNA is estimated at 0.5% per million years. Hence, over the past 10,000 years there has been time for very little change in our genes, possibly 0.005%. Our genes appear to be similar to the genes of our ancestors during the Paleolithic period 40,000 years ago, the time when our genetic profile was established. However, now humans appear to live in a nutritional environment which completely differs from that for which our genetic constitution was selected (Simopoulos and Meester, 2009; Singh *et al*., 2011; Eaton *et al*., 1988; 1998). It was during the last 100-160 years that dietary intakes have changed significantly, causing increased intake of Saturated Fatty Acids (SFA) and (n-6) linoleic acid and decrease in w-3 fatty acids, from grain-fed cattle, tamed at farm houses, rather than meat from running animals. The food and nutrient intake among hunter-gatherers and during Paleolithic period are given in Table 1-3. There is a marked reduction in consumption of w-3 fatty acids, vitamins, antioxidants and amino acids and significant increase in the intakes of carbohydrates, (mainly refined) fat (saturated, trans fat and linoleic acid) and salt compared to the Paleolithic period. The amino acid intake was estimated to be twofold greater (33 Vs 13%) in the Paleolithic diet compared to modern diet (Table 3).

The early diet was rich in essential and nonessential amino acids like glutamate which may have provided the major taste because salt and sugar were unknown during Paleolithic period. Of the four classic tastes; sweet, salty, sour and bitter, salty appears to be of most recent origin. The fifth taste discovered by K Ikeda in 1908 (Umami taste) appears to be the natural taste of the foods available to early man such as human milk, fish, chicken, sea foods, sea weed, all rich in glutamate providing the umami taste (Uneyama *et al*., 2008; McCabe and Rolls, 2007). It may be proposed that the higher risk of cardiovascular diseases and diabetes among people of South Asian origin living anywhere in the world, compared to indigenous populations and other Asian populations, may be due to a lower intake of glutamate among South Asians compared to other populations.

Table 1: Food and nutrient intake among hunter-gatherer and western population

Food and nutrient	Hunter-gatherer	Western population
Energy density	Low	High
Protein	High	Low-moderate
Animal	High	Low-moderate
Vegetable	Very low	Low-moderate
Carbohydrate	Low-moderate (slowly Absorbed)	Moderate-rapidly absorbed
Fiber	High	Low
Fat	Low	High
Animal	Low	High
Vegetable	Very low	High
Total w-3	High (2.3 g day^{-1})	Low (0.2 g day^{-1})
Ratio w- 6: w-3	Low 2.4	High 15-20
Vitamins and minerals	High	Low
Essential amino acids	High	Low

Table 2: Estimated fatty acid consumption in the late Paleolithic period

Sources	Fatty acids (g/day) en 35.65 day^{-1}
Plants	
Linoleic acid	4.28
Alpha-linoleic acid	11.40
Animal	
Linoleic acids	4.56
Alpha-linolenic acid	1.21
Total	
Linoleic acid	8.84
Alpha linolenic acid	12.60
Animal	
Arachidonic acid (w-6) (AA)	1.81
Eicosapentaenoic acid (w-3) (EPA)	0.39
Docosatetraenoic acid (w-6) (DTA)	0.12
Docosapentaenoic acid (w-3) (DPA)	0.42
Docosahexaenoic acid (w-3) (DHA)	0.27
Ratios of w-6/w-3	
Linoleic acid/alpha linolenic acid	0.70
AA+DTA/EPA+DPA+DHA	1.79
Total w-6/w-3	0.79

Table 3: Nutrient composition in the late Paleolithic and current recommendations

Nutrient	Late paleolithic	Current recommendation
Total dietary energy (%)		
Protein	33.0000	12.000000
Carbohydrate	46.0000	58.000000
Fat	21.0000	30.000000
Alcohol	0.0000	moderate alcohol
P/S ratio	1.4100	1.0000000
Cholesterol (mg)	520.0000	300.00000
Fiber (g)	100-1500	30-60.000
Sodium (mg)	690.0000	1100-3300
Calcium, mg	1500-2000	800-16000
Ascorbic acid (mg)	440.0000	600000000
W-6/W-3 ratio	1:0100	1:05.00000

This poses the possibility that glutamate may have beneficial effects on central obesity and metabolic syndrome and can modulate mind-body interactions,

because recent research indicates that glutamate can prevent obesity in mice and has beneficial effects on the hypothalamus, hippocampus and amygdala (Kunio Torii, Asian Nutrition Congress, Singapore, July13-16, 2011).

Treatment of obesity by drug therapy has provided only partial benefit without much influence on morbidity and mortality. However, increased intake of energy in conjunction with decreased physical activity with an underlying genetic predisposition and maladaptation are important factors responsible for the epidemic of obesity and central obesity leading to NCDs. There is only limited evidence demonstrating the role of essential and nonessential amino acids like glutamate on risk of these chronic diseases.

Recent study indicates that activation of ATP-sensitive K+ (KATP) channels by H_2O_2 underlies glutamate-dependent inhibition of striatal dopamine release (Avshalumov and Rise, 2003; Ashford *et al*., 1990). Apart from these factors, quality of foods, mental stress and tobacco intake can also damage mechanisms that predispose obesity and NCDs. Since Mediterranean diet and w-3 fatty acids as well as amino acids like glutamate can influence central mechanisms and psychological behavior, this poses the possibility that these protective factors may be inversely associated with risk of obesity and other NCDs (Simopoulos and Meester, 2009; Singh *et al*., 2011; Eaton *et al*., 1988; 1998; Uneyama *et al*., 2008; McCabe and Rolls, 2007). In this connection, the role of psychological behavior on salivary glands, gut, liver and pancreas and their influence on brain, in relation to fatty acids and amino acids may be of significant importance in the prevention of NCDs (Eaton *et al*., 1988; 1998; Uneyama *et al*., 2008; McCabe and Rolls, 2007; Avshalumov and Rise, 2003; Ashford *et al*., 1990; Bercik *et al*., 2010).

Mind-body axis: The sight, taste and smell of the foods are first few characteristics which are conveyed to the brain as soon as we see, smell and taste the food and begin to eat (Uneyama *et al*., 2008; McCabe and Rolls, 2007). The first point of contact after ingestion of food, initiates a series of homeostatic mechanisms to regulate plasma glucose levels at near physiological concentration during fasting and postprandial periods. The foods masticated, increases salivary secretion which becomes much greater with taste and smell of the foods appreciated by the brain (Uneyama *et al*., 2008; McCabe and Rolls, 2007). The foods ingested stimulate the secretion of ghrelin from the stomach and leptin and incretins from the gut which increase the insulin secretion and initiate a gut-brain-liver axis in response to small amount of triglycerides in the duodenum to rapidly increase insulin secretion. Several experts have long accepted the brain-gut axis and its influence on cardiovascular and gastrointestinal as well as neuropsychiatric function. In animal models, it has been shown, how moderate intestinal inflammation affects complex behavior and how much treatment of such inflammation can influence factors from mind to matter, or brain to gut and the heart (Bercik *et al*., 2010).

We all learned a little about neuro-immunology when we started treating viral hepatitis with interferon, which could trigger severe depression. It is known that circulating proinflammatory cytokines can play a significant role in mood and mood disorders (Bercik *et al*., 2010). This relationship may also contribute to the high prevalence of depression in patients with inflammatory bowel disease as well as among patients with cardiovascular diseases and type 2 diabetes mellitus (Bercik *et al*., 2010). Based on these findings, experiments using the mouse model of moderate intestinal inflammation addressed two questions: first, will intestinal inflammation affect behavior? Second, can clinically-used treatmentof intestinal inflammation/disorders improve the behavioral abnormalities? The animals did not display signs of general malaise, but still exhibited patterns that are a rodent correlate of anxiety. Second, treatments ranging from probiotics to Anti-Tumor Necrosis Factor (TNF) antibodies, differentially altered inflammation and behavior. It is known that blocking TNF signaling blunted inflammation, decreased the level of circulating cytokines and led to normalized behavior (Bercik *et al*., 2010). The glucocorticoid steroid budesonide was not quite as effective, but showed a similar direction of changes. The most interesting results came with the use of probiotics. They decreased markers of gut inflammation, but did not affect circulating cytokine levels. Nonetheless, one strain of Bifidobacteria was about as effective as the immuno-suppressants in improving behavior (O'Mahony *et al*., 2005). It even changed expression of an important neurotrophic factor in a brain region that is important in learning and memory function.

The abdominal vagus consists of an afferent pathway which conveys nutrient information from various abdominal organs to the brain. The efferent pathway conveys information from the brain to the internal organs; gut, liver, pancreas and the adrenals. There is experimental evidence that vagus nerve serves as the neuronal pathway that participates in the connection between the liver and adipose tissue (Cox and Powley, 1981; Uno *et al*., 2006; Das, 2010; Edvell and Lindstrom, 1998). In experiments in the mouse,

adenovirus mediated expression of Peroxisome Proliferative-Activated Receptor (PPAR)-y2 in the liver can induce acute hepatic steatosis. There was a marked decrease in peripheral adiposity, accompanied by increased hepatic energy expenditure and improved systemic insulin sensitivity (Uno *et al.*, 2006).There was also an increased hepatic PPAR-y2 expression as well as decreased fasting plasma glucose, insulin, leptin and TNF-alevels, indicating markedy improved insulin sensitivity. Glucose output from the liver was also reduced. In the sympathetic nervous system, there was an increase in tone as revealed by increased expression of uncoupling protein UCP-1 that uncouples the mitochondrial proton gradient and ATP synthesis and coactivator of PPAR-y2 PGC1a and hormone-sensitive lipase activity and serum free fatty acids, resting oxygen consumption and UCP-1 expression (2), Resection of the hepatic branch of the vagus nerve completely blocked the decrease in peripheral adiposity as well as the increase in serum free fatty acids responsible for endothelial dysfunction. Resting oxygen consumption, UCP-1 expression were also decreased, indicating that the hepatic vagus particularly afferent vagus mediates the effects of PPAR-y2 expression (Uno *et al*., 2006) It is possible to conclude that the hepatic vagus, more specifically the afferent vagus, mediates the effects of hepatic PPAR-y2 expression.

Further studies showed that selective deafferentation of the hepatic branch of the vagus nerve completely blocked the hepatic PPAR y2 expression-induced decrease in peripheral adiposity. The dissection of the hepatic branch of vagus before Thiazolidinedione (TZD) administration reversed the increases in resting oxygen consumption as well as UCP-1 expression in both white and brown adipose tissue. It is possible that the neuronal pathway originating in the liver is also involved in the acute systemic effects of TZD in obese subjects in whom hepatic PPAR-y2 expression is up-regulated (Das, 2010; Edvell and Lindstrom, 1998; Kiba *et al*., 1996; Imai *et al*., 2008). It seems that a neuronal pathway consisting of the afferent vagus from the liver and efferent sympathetic nerves to adipose tissues appears to be involved in the regulation of energy expenditure, systemic insulin sensitivity, glucose metabolism and fat distribution between the liver and the peripheral tissues. Therefore it seems that liver conveys information regarding energy balance to the brain (especially the Ventromedial Hypothalamus (VMH) via the afferent vagus, whereas leptin could be a humoral signal to the brain from the adipocytes. It is possible that brain receives information from several tissues and organs via both humoral and neuronal pathways, which it integrates to produce appropriate response (s) e.g., sympathetic nervous system activation and/or parasympathetic modulation to maintain energy homeostasis. However, brain can also mediate liver and pancreas via the hypothalamus apart from its vagal activity which may be under influence of nutrients (Thaler and Cummings, 2008).

The liver, pancreas and brain axis: Metabolic syndrome, a group of risk factors probably associated with obesity, type 2 diabetes mellitus, Coronary Artery Disease (CAD) and hypertension and insulin resistance, may promote proliferation of pancreatic beta cells, as a compensatory response. The beta cell proliferation may result in hyperinsulinemia. Pancreatic beta cell mass and insulin secretion are under influence of efferent vagal signals (Das, 2010; Edvell and Lindstrom, 1998; Kiba *et al*., 1996). In a experiment in mutant mice, selectively lacking the M3 muscarinic acetylecholine receptor subtype in pancreatic beta cells, there was glucose intolerance with decrease in insulin secretion. However, transgenic mice selectively overexpressing M3 receptors in beta cells of pancreas showed enhanced insulin release and increase in glucose tolerance as well as resistance to diet –induced glucose intolerance and hyperglycemia, indicating that beta cells M3 muscarinic receptors are essential in maintaining proper insulin release and glucose homeostasis ((Das, 2010).

Proliferation of beta cells of pancreas in VMH lesioned animals was associated with obesity, type 2 diabetes mellitus and increased pancreatic weight, DNA content and DNA synthesis. The stimulation of DNA synthesis in association with VMH lesion was completely inhibited by vagotomy which indicated that vagal hyperactivity produced by VMH lesions stimulated cellproliferation of beta cells and acinar cells of rat primarily through a cholinergic receptor mechanism (Edvell and Lindstrom, 1998; Kiba *et al*., 1996). It seems that the vagus nerve, innervating the pancreas, is involved in insulin hypersecretion which may be due to pancreatic beta cell proliferation and hepatic activation of Extracellular Regulated Kinase (ERK) signaling as part of this mechanism. There is a major role of afferent splanchnic and efferent pancreatic vagal nerves in expansion of beta cells of the pancreas during food induced obesity in stretozotocin-induced diabetes (Imai *et al*., 2008). It is possible that hepatic ERK activation transmits signals from the liver to brain, which stimulates the efferent vagus to the pancreas and triggers the pancreatic beta cells proliferation resulting in the hypersecretion of insulin. In later stage of diabetes mellitus, beta cells mass may be reduced, which indicate that therapeutic manipulation of hepatic ERK activation may be useful to trigger pancreatic beta cell mass in diabetes mellitus for regulation of insulin secretion and glucose levels.

Hypothalamus, hyperphagia and obesity: In animal experiments, a VMH lesion causes hyperphagia and excessive weight gain, fasting hyperglycemia, hypertriglyceridemia and impaired glucose tolerance. Intraventricular administration of antibodies to Neuropeptide Y (NPY) abolished hyperplasia in these animals (Gold *et al*., 1972; King *et al*., 1984; Stanley *et al*., 2005). Streptozotocin-induced diabetic animals showed an increase in NPY concentrations in paraventricular VMH and lateral hypothalamic areas. VMH-lesioned rats showed selectively decreased concentrations of norepinephrine and dopamine in the hypothalamus, whereas long-term infusion of norepinephrine and serotonin into the VMH impaired pancreatic islet cell function. After insulin administration, these changes in the hypothalamic neurotransmitters reverted to normal. It is possible that dysfunction of VMH impairs pancreatic beta cell function and induces metabolic abnormalities that are seen in obesity and type 2diabetes mellitus. Tumor Necrosis Factor (TNF)-alpha decreases the firing rate of the VMH neurons and is neurotoxic (Gold *et al*., 1972; King *et al*., 1984; Stanley *et al*., 2005). In VMH –lesioned rats the abundance of (obese) ob mRNA increased after the gain of body weight and marked expression was observed on the 15th day after the VMH lesion was made (Paes *et al*., 2006). These data suggest that the ob gene might be upregulated with fat accumulation even in non-genetically obese animals. There was an increased in the parasympathetic tone after VMH lesion, whereas the sympathetic tone decreases (Paes *et al*., 2006; Sakaguchi *et al*., 1998). These changes are associated with inhibition of lipolysis,that leads to obesity and consequent type 2 diabetes mellitus. There was an increase in Acetylcholinesterase (AChE) activity in liver, pancreas and stomach, known to be vagal targets, of VMH-lesioned obese rats. These findings indicated that AChE activity is enhanced in vagus innervated tissues following VMH lesion-induced obesity (Stanley *et al*., 2005). It was also observed that radical vagotomies, blocked the development of obesity in VMH-lesioned animals, whereas VMH rats with less extensive transactions accumulated substantially more fat. It is possible that the vagus nerve serves as the neuronal pathway from the hypothalamus to the visceral fat and the pancreatic beta cells. This pathway exhibits potential in VMH lesioned animals, in communicating the messages from VMH to produce disturbances in metabolism, leading to obesity and clinical manifestations of type 2diabetes (Cox and Powley, 1981).

In brief, it is clear that specific areas of the hypothalamus and the vagus nerve communications with liver and pancreas to the brain, have a significant role in the regulation of plasma glucose, insulin secretion as well as in the development of obesity and type 2 diabetes mellitus. A glycemic load and high glycemic index can predispose vascular disease and Mediterranean diet can protect against inflamation (Beulens *et al*., 2007; Dai *et al*., 2008).

Omega-3 fatty acids and brain dysfunction: Fish oil and Mediterranean diet have been demonstrated to protect against NCDs; neuropsychiatric disorders, inflammation and metabolic syndrome due to increased consumption of w-3 fatty acids as well as essential and nonessential amino acids and antioxidants (Kwiatek *et al*., 2010; Pella *et al*., 2004; Esposito *et al*., 2004). Singh *et al* reviewed the role of foods and nutrition on brain function in relation to metabolic syndrome indicating that w-3 rich foods and fish oil can modulate brain dysfunction in association with risk factors of metabolic syndrome (Pella *et al*., 2004). In another study among 345 middle-aged twins, adherence to w-3 rich Mediterranean diets was associated with lower levels of interleukins-6 (Dai *et al*., 2008). Mediterranean diets have been found to be protective against inflammation, metabolic syndrome, cardiovascular risk and mortality due to cardiac events (Esposito *et al*., 2004; Singh *et al*., 2010a). In one randomized trial on the effect of a Mediterranean style diet on endothelial dysfunction and markers of vascular inflammation in patients with metabolic syndrome, there was a significant benefit in the intervention group compared to control group (Imai *et al*., 2008). It is not clear whether the effect of diets was due to their influence on cardiovascular risk factors or due to their beneficial effects on brain function (Singh *et al*., 2010b; Moriguchi and Salem, 2003; Freeman, 2000).

The w-3 fatty acids from dietary sources or through supplementation are associated with a reduced risk of impaired cognitive function (King *et al*., 1984), dementia (Heude *et al*., 2003), cognitive decline (Neuringer *et al*., 1994) and improved cognitive development (Willatts, 2002; Gamoh *et al*., 1999), reference memory-related learning (Fontani *et al*., 2005), mood state (Heude *et al*., 2003), increased vigor and sense of well-being (x). These studies strengthen the hypothesis of a direct action of omega-3 fatty acids on brain function. Omega-3 fatty acids can modulate neuronal excitability which influence the function of cell membranes. The signal transduction mechanisms operating at the synaptic level and several pathways with different neurotransmitters such as; serotonin,

noradrenaline, dopamine and acetylcholine are also modulated by these fatty acids. In middle-aged individuals, treatment with w-3 fatty acids improved cognitive performance (Fontani *et al*., 2005). It is possible that an increase in hippocampus acetylcholine level as well as the anti-inflammatory effect of omega-3 fatty acids may be underlying mechanisms for these benefits. The majority of investigators have studied the effects of w-3 fatty acids on biological markers and psychological disorders; depression, schizophrenia, moods and emotional states. However, in a recent study (Fontani *et al*., 2005) the effect of w-3 fatty acid supplementation and lower w-6: w-3 ratio was studied in healthy adults. (Fontani *et al*., 2005) carried out a study on 53 healthy volunteers, 33 males and 20 females ranging between 22-51 years (mean 33+_ 7 years). The subject received a daily supplementation of 4 g of fish oil (1.60 g Eicosapentaenoic Acid (EPA) + 0.80 g Docosahexaenoic Acid (DHA) +0.4 g of other omega-3 fatty acids) for 35 days. Control consisted of 4g olive oil that was indistinguishable by packaging shape or taste. Blood samples showed on day 1 that the AA:EPA ratio was 16.39+- 8.32 mean value in the control group (olive oil group) and 16.17 +- 10.63 in the intervention group that received the fish oil capsules. On day 35 of fish oil administration, there was a large decrease in the AA: EPA ratio (14.26+- 8.87 before w-3 and 4.29 +- 2.60 after w-3; $p<0.001$). However, no significant differences were observed in the control group and no other association were found between the variables studied including age or gender of subject. There was a major improvement in their mood with increased vigor and reduced anger, anxiety and depression states among subjects receiving w-3 fatty acids. An electroencephalogram frequency shift toward the theta and alpha bands was recorded in those tested after fish oil supplementation. It seems that w-3 supplementation is associated with improvement of attention and physiological function particularly those involving complex cortical processing. Omega-3 fatty acids improve neuronal efficiency shown by improvement in reactivity attention, cognitive performance, mood state and by modifying some electrical parameters. It has been known that alpha and beta oscillation reflect cognitive and memory performance which are recorded by electroencephalogram. The theta band reflects episodic memory processes, which leads to the conclusion that short term memory demands are related to an increase in the theta band power, while inaccurate attention switching seems to be combined with an increase in the higher alpha frequencies.

The ratio of w-6/w-3 fatty acid in the cell membrane are responsible for cell function. The preferred ratio in the rat is 4:1 (Yehoda, 2003; Yehoda *et al*., 1999; Helland *et al*., 2003) whereas in men the preferred estimated ratio is 1:1. The consumption of w-3 fatty acid during pregnancy and lactation may favor the later mental development of children (Helland *et al*., 2003). In experimental studies with rats, the ratio of w-6/w-3 fatty acids was most effective in improving learning performance. In rat experiments, the ratio of w-6/w-3 fatty acids of 4:1 was most effective in determining passive avoidance, elevating pain threshold, improving sleep and benefiting thermoregulation as well as correcting learning deficits induced by neurotoxins (Serhan *et al*., 2008).

Omega-3 fatty acids are known to stimulate endocannabinoid receptors present in the brain which produce annandmide-type compounds (e.g., N-Arachidonoyl-Ethanolamine, AEA) responsible for providing satiety. These fatty acids may also produce pro-resolution lipid mediators; resolvins and protectins that are potent resolution agonists which activate cell type –specific programs in neutrophils, macrophages and epithelial cells at multiple levels to accelerate resolution of inflammation by anti-inflammatory cytokines; interleukin-10 and interleukin-4. Both EPA+DHA are precursors of resolvins E-series and D series. DHA can generate protectin D1 which when derived from neural tissue, are called neuroprotectins (Crawford, 1968). Recent findings indicate that resolution is not merely a passive termination of inflammation but rather an active biochemical and metabolic process. The resolution process is implicated by dual acting, anti-inflammatory and pro-resolution lipid mediators, such as lipoxins, resolvins and protectins. These lipid mediators function in the resolution of inflammation by activating specific mechanisms to promote homeostasis. It seems that nutrient act as interface between innate and active immunity (Crawford, 1968)

Coronary artery disease events have a circadian rhythmicity, clustering more in the second quartile of the day (Gal *et al*., 2008; Singh *et al*., 2002). Omega-3 fatty acid supplementation reduces the rate of cardiac events, but its effect on their circadian rhythmicity has not been tested. The Indo-Mediterranean Diet Heart Study (Gal *et al*., 2008; Singh *et al*., 2002) was a single blind randomized study that assessed the effect of a diet rich in alpha-linolenic acid, the parent n-3 fatty acid, on the occurrence of myocardial infarction and sudden cardiac death. Of one thousand subjects of the Indo-Mediterranean Diet Heart Study, focus was placed on the 115 patients from both control and intervention groups in which cardiac events occurred. The timing of cardiac events throughout the day was compared

between the intervention and control groups. The distribution of cardiac events along the four quartiles of the day was compared between groups as well as against an equal distribution. The risk ratio for a cardiac event was lowest between 4:00 and 8:00 for the intervention group. The control group had a higher, rate of events in the second quartile of the day, which deviated from an equal distribution, as expected ($p = 0.013$). In the intervention group, events were equally distributed along the day. {No statistically significant difference was found in daily event distribution between the groups? Is this because effect watered down?}. A diet rich in alpha-linolenic acid may abolish the higher rate of cardiac events, normally seen in the second quartile of the day (Trichopoulou *et al*., 2009; Lorgeril *et al*., 1994; Pella *et al*., 2003). Additional studies are needed to identify the underlying mechanism related to sympathetic and parasympathetic activity and blood pressure variability which may be lying in the brain's suprachiasmatic nucleus that mediate the circadian rhythm (Campese *et al*., 2005; Campese *et al*., 2004).

Essential and nonessential amino acids: Essential and nonessential amino acids consist of hydrogen, nitrogen, oxygen and carbon atoms. These simple molecules play an important role in the human body (Wu, 2009; Hosomi *et al*., 2000; Young and Ajami, 2000; Tomporowski, 2003). The 22 known amino acids, essential and nonessential, affect a broad range of physical and mental processes. Recent studies have witnessed the discovery that amino acids are cell signaling molecules as well as being regulators of gene expression and the protein phosphorylation cascade (Wu, 2009). The majority of the neurotransmitters can influence mind-body interactions and are composed of amino acids. Additionally, amino acids are key precursors for syntheses of hormones and low-molecular weight nitrogenous substances with each having enormous biological importance. Physiological concentrations of amino acids and their metabolites (e.g., nitric oxide, polyamines, glutathione, taurine, thyroid hormones and serotonin) are required for the biological functions in our body. However, elevated levels of amino acids and their products (e.g., ammonia, homocysteine and asymmetric dimethylarginine) are pathogenic factors for neurological disorders, oxidative stress and cardiovascular disease. Thus, an optimal balance among amino acids in the diet and circulation is crucial for whole body homeostasis. There is growing recognition that besides their role as building blocks of proteins and polypeptides, some amino acids regulate key metabolic pathways that are necessary for maintenance, growth, reproduction and immunity. They are called functional amino acids, which include arginine, cysteine, glutamine, leucine, proline and tryptophan. Dietary supplementation with one or a mixture of these amino acids may be beneficial (Wu, 2009; Hosomi *et al*., 2000; Young and Ajami, 2000; Tomporowski, 2003) for ameliorating health problems at various stages of the life cycle (e.g., fetal growth restriction, neonatal morbidity and mortality, weaning-associated intestinal dysfunction and wasting syndrome, obesity, diabetes, cardiovascular disease, the metabolic syndrome and infertility) (Wu, 2009). Amino acids can also optimize efficiency of metabolic transformations to enhance muscle growth, milk production, egg and meat quality and athletic performance, while preventing excess fat deposition and reducing adiposity. Thus, amino acids have important functions in both nutrition and health.

Branched-chain amino acids may have psychological effects as well. Athletes often neglect the importance of mental "toughness," but fatigue can increase errors of omission and commission. According to a review, cognitive performance suffers during physical exercise (Tomporowski, 2003). There is evidence that branched-chain amino acids improved mental performance and decrease fatigue during a boating competition (Wu, 2009). Non-essential amino acids produce similar effects on human physiology. Ingesting ornithine alpha-ketoglutarate increases circulating levels of the non-essential amino acid glutamine which may increases the body size of undersized children without glutamine toxicity. Other non-essential amino acids also have physiological effects. Tryptophan, a precursor of serotonin and melatonin, plays an important role in health and disease and its deficiency may underlie many types of brain disease such as quality of sleep and disturbance in sleep mediated by melatonin.

This study demonstrated the effect of the simultaneous dietary administration of fish protein and fish oil, two macronutrients found in fish meat, on cholesterol metabolism in rats (Hosomi *et al*., 2000). Male Wistar rats were divided into four groups and fed an AIN-93G modified hypercholesterolemic diet with casein (20%) + soybean oil (7%), casein (10%) + fish protein (10%) + soybean oil (7%), casein (20%) + soybean oil (5%) + fish oil (2%) and casein (10%) + fish protein (10%) + soybean oil (5%) + fish oil (2%) for four weeks. Cholesterol metabolism was measured through serum and liver cholesterol assay, fecal cholesterol and bile acid excretion levels and liver mRNA expression levels of enzymes and nuclear receptors involved in cholesterol homeostasis. Dietary fish protein decreased serum and liver cholesterol contents, perhaps through increasing fecal cholesterol and

bile acid excretion and liver cholesterol 7- alpha hydroxylase expression level. Dietary fish oil, on the other hand, decreased liver cholesterol content, perhaps due to the suppression of cholesterol synthesis through a decrease in the 3-hydroxy-3-methylglutaryl-coenzyme A reductase expression level; the serum cholesterol content was unchanged. This study found that the simultaneous dietary administration of fish protein and fish oil, which is achieved by the intake of intact fish muscle, has hypocholesterolemic effects that help prevent hyperlipidemia and atherosclerosis. In another study (Koopmans *et al*., 2011), the ratio of insulin-stimulated glucose versus amino acid clearance was decreased 5.4-fold in diabetic pigs, which was caused by a 3.6-fold decrease in glucose clearance and a 2.0-fold increase in non-essential amino acid clearance. In parallel with the Randle concept (glucose-fatty acid cycle), the present data suggest the existence of a glucose and non-essential amino acid substrate interaction in diabetic pigs whereby reduced insulin-stimulated glucose clearance seems to be partly compensated by an increase in non-essential amino acid clearance whereas essential amino acids are preferentially spared from an increase in clearance.

Glutamate: After the discovery that sodium glutamate was the agent for the palatability of broth from kombu seaweed in 1908 (Professor Kikunae Ikeda of Tokyo Imperial University in Japan), the commercial aspects of free glutamate were noticed by the food industry. He wanted to commercialize the component of kombu seaweed that produces umami taste as seasoning. Umami taste has been established as one of the five basic tastes, distinct from the other basic tastes such as saltiness, bitterness, sourness and sweetness. This taste possibly was known to ancient man because most of the evolutionary foods are rich in glutamate as given in Table 4 and Fig. 1) (Simopoulos and Meester, 2009; Eaton *et al*., 1988; 1998). Behind the establishment of the new taste conception, scientific evidence for the physiological significance of free glutamate-containing foods has accumulated over a century, since its first discovery. Oral stimulation by free glutamate evokes cephalic phase of food digestion, such as an induction of pancreatic juice secretion. In healthy and elderly volunteers, oral intake of free glutamate simulates salivation which is essential for mastication and swallowing (Uneyama *et al*., 2008).

Interactions of w-3 fatty acids and amino acids: It is important that all the cell membranes, mitochondria, DNA, RNA, enzymes hormones and neurotransmitters are made of amino acids. The cell membranes of various cells; like endothelium, macrophages, platelets are composed of amino acids.

Table 4: Evolutionary foods rich in glutamate

Nonvegetarian	Vegetarian
Beef and	Soyabeans and beans
Chicken	Corn,
Fish	Green peas,
Cheese	Tomato,
Human breast milk	Spinech,
Sea foods;	Cabbage,
krabs, scallop	mushroom,
	Onion
	Sea weeds;
	Dried lever,
	Kelp (konbu)

All the antioxidant enzymes; catalase. glutathione peroxidase,ceruloplasmin and neurotransmitters; adrenaline, noradrenaline, serotonin, cortisol, acetylecholine, prostaglandins as well as gut hormones; ghrelin, leptin, cholycystokinin, incretins, brain derived neurotrophic factor and insulin are made of amino acids. It is possible that fatty acids in conjunction with antioxidants, vitamins and minerals interact with amino acids in the synthesis and release of various enzymes and hormones. Majority of the magnesium and coenzyme Q10 present in the body are intracellular and present in the inner cell membrane. W-3 fatty acids; EPA, DHA are incorporated in the phospholipids of the cell membrane of various cells which are made up of amino acids. Deficiency of w-3 fatty acids and amino acids may cause dysfunction of cell membranes, resulting in increased susceptibility of these cells to enhance coagulation which predisposes athero-thrombosis.

Endothelial cell damage due to deficiency of amino acids may be the first step, initiating the process, leading to increased activation of macrophases, platelets and red blood cells; causing atherogenesis and thrombosis.

Effects of diet on risk of cardiovascular disease: Western diets are characterized by high omega-6 and low omega-3 fatty acid intake, whereas during the Paleolithic period when the human's genetic profiles was established, there was a balance between omega-6 and omega-3 fatty acids as well as amino acids. Therefore, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected. Cohort studies have demonstrated that European vegetarian diets of Seventh-Day Adventists, Mediterranean diet (fruit, vegetables, nuts, whole grains, olive oil, wine fish, chicken), Japanese diets; (vegetables, raw fish, whole rice), Indo-Mediterranean diet(whole grains, fruits, vegetables, nuts and mustered oil) and the French paradox diet (vegetables and wine) are protective against cardiovascular disease, diabetes and cancer.

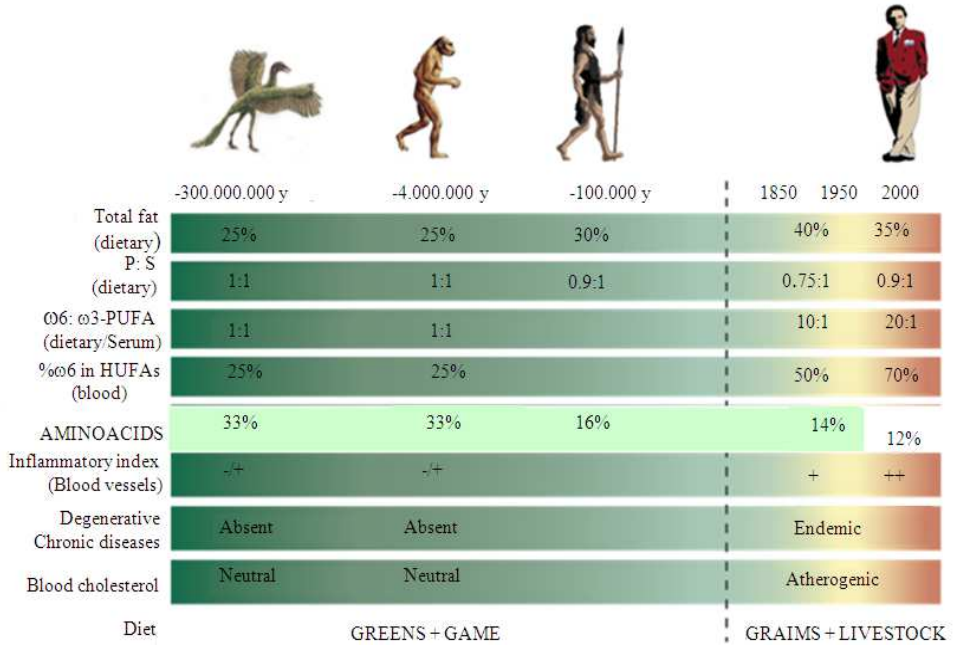

Fig. 1: Nutrient intake in Paleolithic period, huntergatherers and modern man

All these diets are rich in amino acids as well as w-3 fatty acids, however, only omega-3 fatty acids has been considered in the mechanism of benefit without any consideration for amino acids.

Effect of glutamate on brain function: Gustatory and anticipatory cephalic stimuli during a meal yield nutritional information and aid efficient food digestion (Uneyama *et al*., 2008; McCabe and Rolls, 2007; Young and Ajami, 2000; Tomporowski, 2003; Koopmans, 2011; Uematsu *et al*., 2009; 2010; Kitamura *et al*., 2011). There is evidence that mammals, including humans, can detect the amount of dietary protein and its quality via cephalic relay to initiate proper digestion in the upper gastrointestinal tract. Apart from gustatory stimuli, visceral sensing by the abdominal vagus conveys primary afferent nutritional information from the digestive system to the brain. Further evidence showed that abdominal vagal afferents, which were innervated into the stomach and intestine sending information to the brain, were activated by luminal glutamate (Uneyama *et al*., 2008; McCabe and Rolls, 2007). There is existence of a glutamate signaling system, metabotrophic glutamate receptors in the gastrointestinal tract (Uneyama *et al*., 2008; McCabe and Rolls, 2007; Kitamura *et al*., 2011). Luminal glutamate in the stomach and intestine provides the efferent reflection of the abdominal vagus, supporting the modulation of exocrine and endocrine excretion during digestion. These results strongly indicate that glutamate has regulatory effects on the food digestive processes through the gut nutrient-sensing system. Glutamate plays physiological and nutritional roles and initiates digestion in the stomach as well as anticipating subsequent processes in the small intestine and the liver (Uematsu *et al*., 2009; 2010; Kitamura *et al*., 2011). The physiological significance of dietary free glutamate in the regulation of gut function, focusing on the visceral sensation from the stomach appears to be very interesting.

Increased intake of salt>5 g day^{-1} and an excess of sugar may be associated with cardiovascular diseases and cancer. Increased consumption of sugar also increases the risk of obesity, metabolic syndrome, Type 2 diabetes mellitus, gall bladder diseases, bone and joint diseases as well as degenerative diseases of the brain. Several experts advise to decrease the intake of salt and sugar by Substituting Monosodium Glutamate (MSG) which makes the foods highly palatable and decreases the need for salt and sugar. In one study among 11 elderly Japanese, addition of monosodium glutamate to rice gruel for 2 months was associated with; improvement in nutritional status and quality of life as well as increase in lymphocyte count indicating better immunity (Toyama *et al*., 2008). No effect was noticed on mean body mass index, blood pressures, serum creatinine and liver enzymes. These findings indicate that glutamate may be supplemented and substituted for salt and sugar, to enhance palatability of foods. In a

experimental study in male Sprauge Dawley rats, glutamate consumption suppressed weight gain, fat deposition and leptin levels (Kondoh and Torii, 2008).

The glutamate supplement was 1% MSG solution which actually showed weight gain reduction when given with high fat diet compared to no mono sodium glutamate with high fat diet. In another experimental study of 36 mice, MSG was administered with low and high fat diets and water with and without MSG (Ren *et al*., 2011). After 16 weeks follow up, no effect was observed on weight gain and 1.0% MSG solution was greatly preferred over plain water. Mice fed LF (low fat) diets, having access to MSG showed a consistent preference.

The intermap study of 752 Chinese, mean age 50 y, MSG intake was positively associated with overweight (He *et al*., 2008). However, there are many limitations in the methodology of this study. Prevalence of overweight was significantly higher in MSG users than nonusers, which may be because they eat possibly, more food and are less physically active because assessment of occupational physical activity is open to bias. The other important weakness was that the sample size was to small (n = 752). Dietary intakes were obtained by 24 h recall which is open to bias and mistakes in the assessment. We need to assess dietary intake by 7 days food intake dietary diaries or by weighing of foods for 7 days for finding out accurate intake of foods. The MSG intake can vary around the 7 week days. Cross-sectional surveys are open to bias by the experts recording the data and hence prospective cohort study is necessary to find out the association of MSG intake with obesity.

Dietary intakes of glutamate were studied among approx.1300 Chinese, mean age 55 years, using a food frequency questionnaire for 5 years (Shi *et al*., 2010). The findings indicated that when dietary patterns are accounted, no association was observed between MSG intake and weight gain. Further studies are necessary to find out the beneficial effects of glutamate on various gut hormones and other body systems.

In brief, the balance of omega-6/omega-3 fatty acids as well as amino acids is an important determinant in decreasing the risk for central obesity, type 2 diabetes mellitus, Coronary Artery Disease (CAD), both in primary and secondary prevention studies (Singh *et al*., 2010c; Lorgeril *et al*., 1994; Singh *et al*., 2009). Increased dietary intake of linoleic acid leads to oxidation of LDL, platelet aggregation and interferes with the incorporation of EPA and DHA into cell membrane phospholipids and a decrease in HDL. Both omega-6 and omega-3 fatty acids influence gene expression which may be modulated by amino acids. EPA and DHA have the most potent anti-inflammatory effects that may be enhanced by amino acids. Inflammation is at the base of many chronic diseases, including coronary heart disease, diabetes, arthritis, cancer, osteoporosis, mental health, dry eye disease and macular degeneration. Dietary intake of omega-3 fatty acids may prevent the development of disease, particularly in persons with genetic variation, as for example in individuals with genetic variants at the 5-LO (5-lipoxygenase) pathway and the development of CAD. The omega-3 fatty acids from dietary sources or through supplementation are associated with a reduced risk of impaired cognitive function, dementia and improve cognitive development, mood state, increase vigor and a sense of well-being, suggesting a direct action of omega-3 fatty acids on the CNS. Chronic non-communicalbe diseases are multigenic and multifactorial. It is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree or severity of disease resulting from the genetic predisposition. It is essential to increase the omega-3 and decrease the omega-6 fatty acid intake in order to have a balanced omega-6 and omega-3 intake in the background diet during conducting clinical trials. The dietary intake and plasma levels or red cell membrane phospholipids of w-3 fatty acids and amino acids should be determined before and after the intervention study. The role of amino acids in the diet rich in w-3 fatty acids could be additive. Glutamate appears to be rich in all superfoods used during Paleolithic period which may have antidepressant like activity (Singh *et al*., 2010c; Tee and Hassan, 2011). These foods may also modulate brain configuration during emotional behavior (Corona *et al*., 2011).

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