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Review Article

Role of stress and inflammation on neurotransmission affecting signalling release of dietary acetylcholine, role of serotonin to induce normal sleep cycle.

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Abstract

Mental health has seen to apprehend the burden on national healthcare after escalating event like COVID where need for awareness, understanding its role in behaviour and medical care requirements surged. However, socioeconomic disparity, stress of lockdown, work from home, traumatic brain injury happening due to death and fear accelerated the need to focus on mental wellness. The burden of Mental diseases has almost doubled since 1990, and the uncertainty to predict the growth rate prevails. Stress has been a major activator factor to increase the burden of all inflammatory response happening at cellular level as stress affects our Hypothalamus-Pituitary- Adrenal Axis and Gut-Brain Axis [2]. Inflammation has become major cause in disturbing our cellular gradient potentiality, membrane permeability and thereby causing disruptions in major signalling biochemical pathways which affect our thought process, dietary choices and overall wellbeing.

Exposure to radiations, chemical toxins, inhaling polluted air, dependence on convenience foods and lack of physical activity are few major contributing factors that are affecting our secondary chemical metabolites resulting in primary damage of our cellular membrane. Acetylcholine a neurotransmitter is highly affected with cellular gradient disturbances thereby affecting our nervoussystem and overall behaviour of our body. Serotonin a neurotransmitter to induce sleep is hampered due to insufficient tryptophan content in our diet and inability to digest tryptophan rich foods due to gradient and electrochemical charges imbalances happening at our membrane levels.Through this article an attempt has been made to simplify the understanding of stress and inflammation on primary function of tissue membrane in energy and metabolism which initiates a series of secondary biochemical chain reactions.

Keywords: mental health; brain, neurotransmitters; acetylcholine; serotonin; sleep; diet composition; quality nutrition; gut brain axis; hypothalamus pituitary adrenal axis

Introduction

According to a survey 792 million people were suffering with some mental illness and most commonprevailing are anxiety and depression. Contributing factors were socioeconomic disparity, inequality, lack of education, unhygienic living conditions, nutrient deficit diet. Our internal biochemical pathways are highly sensitive towards quality of what we think, breathe and consume on daily basis.The adverse effects of our ill health care been heightened when we enter our 30s due to work and financial pressure which affects our neurotransmission and signaling pathways. Stress is defined asan absolute response that is generated in our Central Nervous System (CNS) and distributed using our neurotransmission network throughout the body which is regulated by secretion and diffusion process. Many external factors like infection, pollution, unhygienic conditions and foods have played major role in disturbing our inner metabolic environment resulting into inflammatory responses (headaches, acidity and bloating), changed behavior (depression, anxiety, hypersensitivity), dietary preferences (cravings, unbalanced proportion, junk foods over healthy foods), are few observable changes that we have witnessed more especially post pandemic. Many scientists and researchers are presently working to find a concrete solution either drugs, tools or foods that can help in preventing inflammatory responses generated due to unhealthy eating habits, however as many biochemical processes like membrane permeability, gradient imbalances, genetics, metabolic rate and metabolic compounds are compromised during inflammatory responses. Two parallel axis namely Hypothalamus-Pituitary-Adrenal Axis and Gut-Brain Axis that

determines our anatomical and physiological performances creates a resonating chain reactions under stress and inflammatory responses.

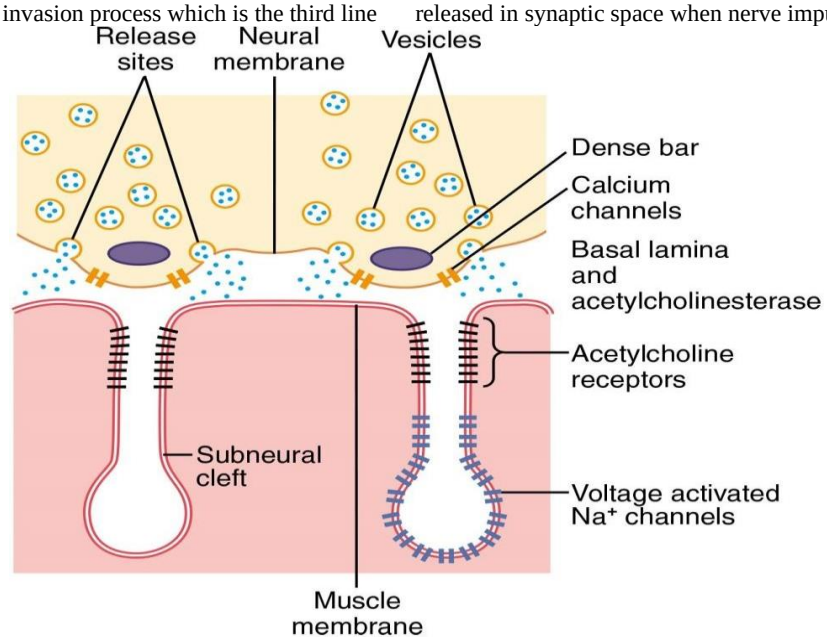
Inflammation and Tissue Injury

When any viral, bacterial, chemical, heat, trauma affects and damages our tissue in any stressful events numerous substances are released that brings in secondary changes to the adjacent undamaged tissues, the process is termed as Inflammation [1]. Characteristics of Inflammation includes 1) Vasodilation of blood vessels(excess blood flow) 2)Increase permeability of capillaries causing chemical membrane gradient imbalance 3)Fluid clots are generated due to interaction with fibrinogen and other proteins from the leaking capillaries 4)Migration of granulocytes and monocytes into tissue 5)Swelling of the tissue [1]. The chemical substances produced due to tissue damage and cause the above reactions are histamine, bradykinin, serotonin, prostaglandins, plasma proteins, lymphokines, these together activate, and they initiate the tissue macrophage system our body's first defence system against infection [1]. The phagocytic action of macrophages begins within few minutes of inflammation depending on the site of inflammation like histiocytes in subcutaneous tissues, alveolar in lungs and microglia in the brain.[1] Based on the invading neutrophil and its adhesion molecules second line of defence is initiated within an hour of infection where pool of neutrophils begin their scavenging activity.[1] When the neutrophilia condition is attained monocytes from the blood enters the inflamed tissue and activates second macrophage invasion process which is the third line of defence. [1] Lastly increase production of granulocytes and monocytes by bone marrow if continued as stimulus from the inflamed tissue the process lasts for months and years resulting in non-healing conditions. During this defence activation period control chemicals like tumor necrosis factor(TNF), interleukin-1(IL-1), granulocyte-monocyte colony-stimulating factor(GM-CSF) and monocyte colony stimulating factor (M-CSF) are formed that combines to proceed the formation of white blood cells that helps in eliminating the cause of inflammation.

Role of Stress on Central Nervous System

Stress has become an inevitable process in today's lifestyle and pandemic was a catalyst to this process where stress is defined as absolute response to any claimed change that body experiences. The HPA axis and Sympathetic Nervous System (SNS) are the peripheral limbs of stress which are activated inside the brain and are transported to lymphatic system through neurons and neurotransmitters [2]. Nervous system is highly complex messenger network system that controls our thinking process and actions resulting from our thought process. Cell membranes comprises of positive charge and negative charge, nerves and muscle cells membranes are involved in rapid electrochemical impulse generation that are used to transmit our signals, however during stressful conditions the diffusion potentials at cell membrane is disturbed due to which nerve action potential is hampered.

Neuromuscular junctions contain proteins named acetylcholine that are released in synaptic space when nerve impulse passes by.[1]



Source [1]

Fig. (1) *Shows the release of acetylcholine from synaptic vesicles at the neural membrane of the neuromuscular junction.*

Dietary Acetylcholine (ACh):

Acetylcholine was first discovered in 1914 by Ewins in non-animal cells and since then many scientists started researching on its role in plant metabolism. In 1966 Cumming and Wagner first time noted that in plants just like animals, bioelectric potentials arose in response to light stimuli.[3]. Table 1 indicates Acetylcholine occurrence in higher plants (ACh). The chemical formula of Acetylcholine is $(CH3COOCH2CH2N^{+}(CH3)3)$ and its molecular mass is 146.2 and is highly dependent on the pH level. The stability of ACh solutions decrease with increase in pH levels and inbasic solutions the substance hydrolysis rapidly to choline and acetic acid.[3] Thus ACh is highly sensitive to pH and also it was noted that at temperature $25^{O}C$ and pH7.0 decomposition takes place in about 20days but at pH12 it only takes 12seconds, indicating that along with pH temperature also plays vital role in decomposition of ACh.[3]

Occurrence of acetylcholine (ACh) in higher plants

Family	Species	Site	Reference
Amaranthaceae	*Amaranthus caudatus* L.	aerial parts	Hartmann & Kilbinger (1974b)
Anacardiaceae	*Rhus copallina* L.	leaves	Miura & Shih (1984)
Aquifoliaceae	*Ilex opaca* Ait.	leaves	Miura & Shih (1984)
Betulaceae	*Betula pendula* Roth.	leaves	Miura & Shih (1984)
Caprifoliaceae	*Lonicera japonica* Thunb.	leaves	Miura & Shih (1984)
	Viburnum dilatatum Thunb.	leaves	Miura & Shih (1984)
Chenopodiaceae	*Spinacia oleracea* L.	leaves, shoots	Appel & Werle (1959) Hartmann & Kilbinger (1974b)
Compositae	*Helianthus annuus* L.	shoots, roots	Hartmann & Kilbinger (1974b)
	Porophyllum lanceolatum DC	leaves, shoots, roots	Horton & Felippe (1973) Ledeira et al. (1982b)
	Xanthium strumarium L.	shoots, roots	Ledeira et al. (1982b)
Cruciferae	*Brassica oleracea* v. *gongylodes* L.	aerial parts	Holtz & Janisch (1937)
	B. oleracea v. *napobrassica* L.	aerial parts	Holtz & Janisch (1937)
	Capsella bursa-pastoris L.	aerial parts	after Marquardt & Falk (1957)
	Sinapis alba L.	shoots, roots	Hartmann & Kilbinger (1974b) Ledeira et al. (1982a)
Cucurbitaceae	*Cucumis anguria* L.	aerial parts	Ledeira et al. (1982b)
	C. sativus L.	aerial parts	Holtz & Janisch (1937) Verbeek & Vendrig (1977)
	Cucurbita pepo L.	shoots, roots	Hartmann & Kilbinger (1974b)
Euphorbiaceae	*Codiaeum variegatum* Blume.	leaves	Miura & Shih (1984)
Gramineae	*Avena sativa* L.	aerial parts	Tretyn & Tretyn (1990)
	Stipa tenacissima L.	leaves	Antweiler & Pallade (1972)
	Zea mays L.	leaves	Miura & Smith (1984)
Hamamelidaceae	*Liquidambar styraciflua* L.	leaves	Miura & Shih (1984)
Leguminosae	*Albizia julibrissin* Durazz.	leaves, seeds	Satter et al. (1972)
	Vigna sesquipedalis (L.) Fruw.	hypocotyl	Hoshino (1983b)
	Phaseolus aureus Roxb.	shoots, roots, seeds	Jaffe (1970) Miura & Shih (1984)
	P. vulgaris L.	shoots, roots	Hartmann & Kilbinger (1974b)
	Pisum sativum L.	leaves, shoots, roots, seeds	Hartmann & Kilbinger (1974b) Jaffe (1972) Miura & Shih (1984) Roshchina & Mukhin (1985)
Lemnaceae	*Lemna gibba* G3 L.	whole plants	Hoshino & Oota (1978)
Loranthaceae	*Viscum album* L.	shoots	after Marquardt & Falk (1957)
Moraceae	*Artocarpus champeden* Merr.	leaves, seeds, fruits	Lin (1955)
	A. integra Merr.	leaves, seeds, fruits	Lin (1957)
Pinaceae	*Pinus silvestris* L.	aerial parts	Kopcewicz et al. (1977)
Plantaginaceae	*Plantago regelii* Decne.	leaves	Miura & Shih (184)
Polygonaceae	*Rumex obtusifolius* L.	aerial parts	Ledeira et al. (1982b)
Rosaceae	*Crataegus oxyacantha* L.	leaves, flowers, fruits	Fiedler et al. (1953)
	Prunus serotina Ehrh.	leaves	Miura & Shih (1984)

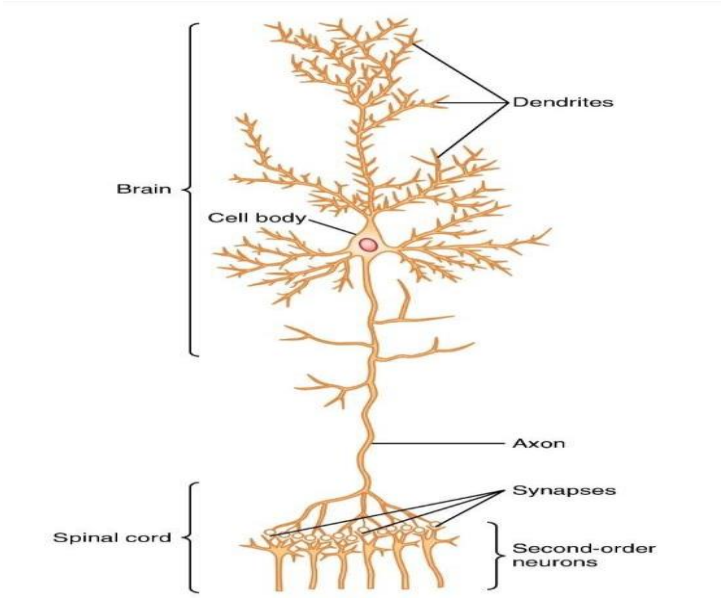
Continued

Family	Species	Site	Reference
Salicaceae	*Populus grandidentata* Michx.	leaves	Miura & Shih (1984)
Scrophulariaceae	*Digitalis ferruginea* L.	shoots	Tulus et al. (1961)
	D. lauta L.	leaves	Neuwald (1952)
	D. purpurea L.	leaves	Neuwald (1952)
Smilacaceae	*Smilax hispida* Muhl.	leaves	Miura & Shih (1984)
Solanaceae	*Solanum tuberosum* L.	tubers	Marquardt et al. (1952) Oury & Bacq (1938)
Umbelliferae	*Daucus carota* v. *sativa* L.	leaves	Holtz & Janisch (1937)
	Carum copticum Benth.	seeds	Devasankaraiah et al. (1974)
Urticaceae	*Girardinia heterophylla* Gandich	leaves	Saxena et al. (1966)
	Urtica dioica L.	leaves, shoots, roots	Collier & Chesher (1956) Emmelin & Feldberg (1949)
	U. parviflora Roxb.	leaves, stinging hairs	Saxena et al. (1965)
	U. urens L.	leaves, shoots, roots	Emmelin & Feldberg (1947)

Source: [3]

Nervous System:

The Central Nervous System (CNS) contains more than 100billion neurons which receives millionsof bits of information from different sensory nerves and organs that are integrated and determines responses to be made by the body.[1] Fig. 2 shows the structure of neuron with its important functional parts.

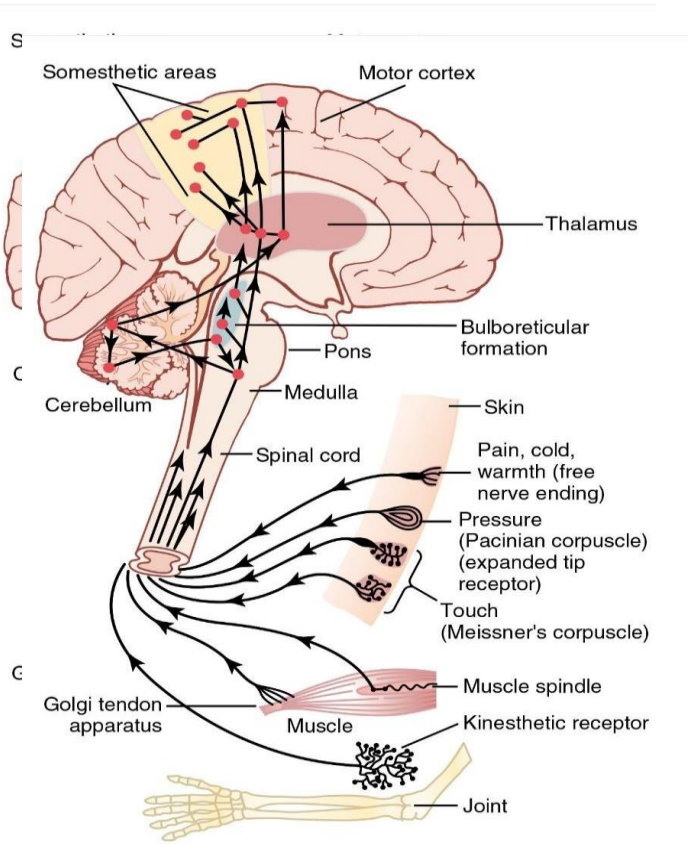


Source: [1]

Most of the information that our brain receives through neurons are generated from sensory excitedreceptors like eyes, ears, smell and touch. These experiences determine our response reactions tohappen instantly or store in memory for minutes, weeks and years. The motor functions of the body are controlled by contraction of skeletal muscle, smooth muscle guarding internal organs and secretion of hormones in exocrine and endocrine glands in the body. CNS main role is processing the information by balancing sensory and motor receptors through synapses (Synapses is the junction point from one neuron to next)i.e. synapses determines the direction of the nervous signals and are controlled by inhibitory and facilitatory signals from other areas of CNS. There are two typesof synapses 1) Chemical and 2) Electrical most of all the synapse uses chemical synapses that release neurotransmitters which acts on receptor proteins in the membrane. More then 40 neurotransmitters have been identified but widely explored ones are Acetylcholine, Norepinephrine, Epinepherine, Histamine, Gamma-aminobutyricacid (GABA), Glycine, Serotonine and Glutamate.

Electric synapses are characterised by direct open fluid channels that conduct electricity from one cell to next and are made up of small tubular protein structures called “Gap Junctions” [1]. Fig. 3 depicts the somatosensory response generated from the excited sensory receptors throughout thebody.

Source: [1]



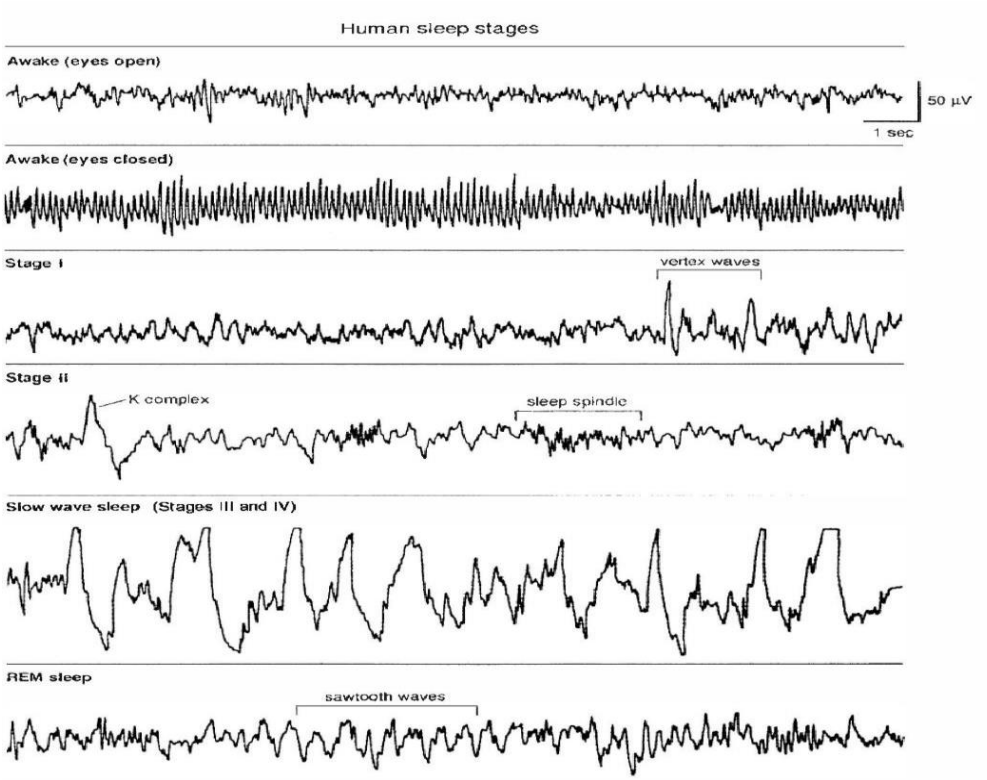
Traumatic Brain Injury:

Trauma is defined as emotional response generated due to accident, physical abuse, death or natural disasters. Traumatic Brain Injury is defined as damaged caused by external forces like violent blow, bump or blast that damages our brains protective capacity.[4] Based on the damage TBI can be classified as Mild, Moderate or Severe and the effect can be temporarily, few days, weeks, months or lifetime. Clinical symptoms of TBI are headaches, dizziness, nausea, fatigue, sleep disruptions, hearing and visual disturbances.[4] TBI is classified as primarily that affects the cognitive functionality namely attention deficient, memory problems and white matter diffusion while secondary injury affects the behavioural patterns like irritability, mood swings, aggressive, impulsive and self-centred behaviour. Apart from cognitive and behavioural disruption also neuroinflammatoryresponses increases the chances of neurodegenerative diseases like Schizophrenia, Parkinson, Alzheimer's, Dementia which are often found in females due to dysfunction of motor nervous system, older adults due to low socioeconomic status. The moment TBI impacts a chain reaction from primary injury activates the secondary chemical avalanche resulting in disruption in blood- brain-barrier (BBB)(Neuronal cell death), oxidative stress(accumulation of Reactive oxygen species(ROS) and reactive nitrogen species(RON)), mitochondrial dysfunction, excitotoxicity(accumulation of intracellular glutamate to extracellular space) and inflammation.[4]

Importance of Sleep:

Sleep is defined as unconscious state of body that can be brought to conscious state by sensory stimuli. It is a passive process associated with amplitude of brain activation. Functionality of sleep isto bring restorative, homeostatic function and normalized thermoregulation and energy conservation.[5] There are two physiological state of sleep 1) Non-Rapid Eye Movement (NREM) 2)Rapid Eye Movement (REM). In order to understand the two types of sleep and the function of brain an electroencephalogram helps in better understanding and Fig. 4 shows an electroencephalogrampatterns of stages of human sleep and wakefulness followed by Table 2 depicting electrophysiological criteria.

Source: [5]



Stages of Sleep—Electrophysiological Criteria

	Electroencephalogram	Electrooculogram	Electromyogram
Wakefulness	Low-voltage, mixed frequency activity; Alpha (8–13 cps) activity with eyes closed	Eye movements and eye blinks	High tonic activity and voluntary movements
Nonrapid eye movement sleep			
Stage I	Low-voltage, mixed frequency activity; Theta (3–7 cps) activity, vertex sharp waves	Slow eye movements	Tonic activity slightly decreased from wakefulness
Stage II	Low-voltage, mixed frequency background with sleep spindles (12–14 cps bursts) and K complexes (negative sharp wave followed by positive slow wave)	None	Low tonic activity
Stage III	High-amplitude (≥75 μV) slow waves (≤2 cps) occupying 20 to 50% of epoch	None	Low tonic activity
Stage IV	High-amplitude slow waves occupy >50% of epoch	None	Low tonic activity
REM sleep	Low-voltage, mixed frequency activity; Saw-tooth waves, theta activity, and slow alpha activity	REMs	Tonic atonia with phasic twitches

cps, cycles per second; REM, rapid eye movement.
(Criteria from Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects.* UCLA, Los Angeles: Brain Information Service/Brain Research Institute; 1968, with permission.)

Source: [5]

Table 3 *is created after refering [5] to better understand the physiological processes happening at both the sleep state and how inhibition and activation of neural network located at the brainstem is associated with neurotransmitter namely serotonin.*

NREM	REM
Peaceful state with dreams that are lucid and purposeful	Near to awake state with dreams that are abstract and bizarre

Pulse rate, Respiration rate,Blood pressure is low	Pulse rate, Respiration rate, Blood pressure ishigh along with high brain oxygen requirement
Resting muscle potential is low	Near to total paralysis of skeletal(postural)muscles
Hemothermic Regulation	Thermoregulation altered

Dietary Sources of Tryptophan Precurssor of Serotonin:

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter synthesized by very limited number of cells in brainstem raphe nuclei. The physiological role of 5-HT as CNS modulator has been obstructed due to diversification of serotonergic receptors and its transmission which is mostlyparacrine in nature.[6] The synthesis of brain 5-HT synthesis rate is physiologically regulated by substrate l-tryptophan(Trp) levels with enzyme Tryptophan hydroxylase(TPH)2 acting as rate limiting enzyme. An experiment on rats conducted by *Ogiso E.,et.al*[6] in 2012 strongly suggested that 5-HT has a significant role on circadian rhythm of sleep-wake cycles. Tryptophan is an amino acid that is crucially obtained from dietary sources and is metabolised intracellularly in different tissues to perform numerous physiological functions. It is found circulating in plasma and blood withits binding protein albumin, however free form of tryptophan content is just 10-12% and many drugsor fatty acids have shown to modify binding of tryptophan to albumin.[7] There are two types of tryptophan L-Tryptophan produced during food processing and D-Tryptophan produced by gut microbiome.[8] Degradation of tryptophan into kynurenine in presence of Indoleamine2,3 dioxygenase in immune cells plays vital role during infections, inflammations and preganancy.[7] In order to understand the bioavailability of tryptophan that can enter the complex protein metabolism pathway numerous analytical methods were proposed to understand optimal pH and temperature requirement. Many research has shown that protein hydrolysates are beneficiary during tissue repair mechanism due to its increase absorption ability based on which tryptophan hydrolysates arewidely used in dietary supplements and food fortification industries. Fig. 5 shows common cereals and millets along with grain and legumes that contain tryptophan.[12] The RDA of tryptophan is in between 250mg – 425mg/day which means dietary intake of 3.6-6.0mg/kg of the body weight.[13] The article also mentions that hydroslyte form of tryptophan has better absorption functionality pure tryptophan.[7]

Food Name	Tryptophan
(All values are expressed in g per 100g protein)	
CEREALS AND MILLETS	
Amaranth seed, black *(Amaranthus cruentus)*	1.50
Amaranth seed, pale brown *(Amaranthus cruentus)*	1.69±0.10
Bajra *(Pennisetum typhoideum)*	1.33±0.30
Barley *(Hordeum vulgare)*	1.28±0.07
Jowar *(Sorghum vulgare)*	1.03±0.21
Maize, dry *(Zea mays)*	0.57±0.12
Maize, tender, local *(Zea mays)*	0.58±0.07
Maize, tender, sweet *(Zea mays)*	0.70±0.05
Quinoa*(Chenopodium quinoa)*	1.25
Ragi *(Eleusine coracana)*	0.91±0.30
Rice flakes *(Oryza sativa)*	1.11±0.13
Rice puffed *(Oryza sativa)*	1.07±0.29
Rice, raw, brown *(Oryza sativa)*	1.00±0.17
Rice, parboiled, milled *(Oryza sativa)*	1.15±0.06
Rice, raw, milled *(Oryza sativa)*	1.27±0.14
Samai *(Panicum miliare)*	1.35±0.10
Varagu *(Setaria italica)*	1.32±0.19
Wheat flour, refined *(Triticum aestivum)*	1.04±0.16
Wheat flour, atta *(Triticum aestivum)*	0.99±0.16
Wheat, whole *(Triticum aestivum)*	1.40±0.10
Wheat, bulgur *(Triticum aestivum)*	1.11±0.15
Wheat, semolina *(Triticum aestivum)*	1.04±0.12
Wheat, vermicelli *(Triticum aestivum)*	1.07±0.09
Wheat, vermicelli, roasted *(Triticum aestivum)*	0.99±0.14

Food Name	Tryptophan
(All values are expressed in g per 100g protein)	
GRAIN LEGUMES	
Bengal gram, dal *(Cicer arietinum)*	1.09±0.25
Bengal gram, whole *(Cicer arietinum)*	0.95±0.07
Black gram, dal *(Phaseolus mungo)*	1.07±0.12
Black gram, whole *(Phaseolus mungo)*	0.98±0.14
Cowpea, brown *(Vigna catjang)*	1.05±0.03
Cowpea, white *(Vigna catjang)*	0.92
Field bean, black *(Phaseolus vulgaris)*	0.73
Field bean, brown *(Phaseolus vulgaris)*	0.78
Field bean, white *(Phaseolus vulgaris)*	0.89±0.07
Green gram, dal *(Phaseolus aureus)*	1.24±0.42
Green gram, whole *(Phaseolus aureus)*	1.02±0.14
Horse gram, whole *(Dolicus biflorus)*	1.08±0.25
Lentil dal *(Lens culinaris)*	0.81±0.07
Lentil whole, brown *(Lens culinaris)*	0.76±0.04
Lentil whole, yellowish *(Lens culinaris)*	0.75
Moth bean *(Vigna aconitifolia)*	0.92±0.04
Peas, dry *(Pisum sativum)*	0.86±0.19
Rajmah, black *(Phaseolus vulgaris)*	1.22
Rajmah, brown *(Phaseolus vulgaris)*	1.04±0.13
Rajmah, red *(Phaseolus vulgaris)*	1.05±0.27
Red gram, dal *(Cajanus cajan)*	0.71±0.11
Red gram, whole *(Cajanus cajan)*	0.75±0.17
Ricebean (*Vigna umbellata*)	0.82
Soya bean, brown *(Glycine max)*	1.59±0.26
Soya bean, white *(Glycine max)*	1.68

Source: [12]

Future Work:Thus, as observed inflammatory response that are created due to tissue injury, infection or toxic chemical ingestion are the primary cause of overall health damage. Most of the diseases that are engulfing presently are causing harmful effect on our tissue membrane which disturbs our haemostasis, cause inflammation of the cell and are remodelling our tissue repair process that creates a challenging tasks for drug formulation. Study on rodents was conducted by[9] that showedhow toxicokinetics and toxicodynamics follows the same rule of absorption, distribution, metabolism and excretion that interfers with our signalling pathways, growth factors and hormone secretion.

This study also showed how nutrients like protein, carbohydrates and lipids affects the toxic responses generated and affecting our energy metabolism at cellular levels. Another study was conducted on membrane composition that indicated that manipulation of membrane composition depending on size of the body molecular activity of membrane proteins are also affected.[10] Thus much work on role of nutrition, inflammatory genes suppression, toxin evaluation needs to be conducted based on geographic, demographic, socioeconomic differences which can help in future design of some novel functional foods that can bring a communicating pathway to communicate with all inflammatory non communicable diseases.

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