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Stress Modulating Nutrition Effect on Hypothalamus Pituitary Adrenal Axis and Gut Brain Axis

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Abstract

Nutrition has played a vital role indetermining the health of a living cell. Food is defined as complex combined structure of primary and secondary compounds that are responsible for initiation of intrinsic biochemical pathways which builds our internal fortress during foreign particle invasion. Nutrients like Na+, K, Cl, have been studied to create electrochemical gradient for the energy metabolism thereby interacting with our hypothalamus. Hormones synthesized and released in minute concentration are responsible for alignment of our Hypothalamus-Pitutary-Adrenal axis (HPA axis). Normal microbiota having a symbiotic relationship with human body constantly interacts with HPA axis and has developed a network communication called Gut Brain Axis (GBA) which experiences the intramolecular force in the form of food depending upon individual diet preferences. Microbial factors, physiological factors, cellular factors, Humoral factors, Constitutional factors, Socioeconomic factors are combined in order to determine our mental health and gut health contributing to our overall interior and exterior makeup. In present lifestyle stress has become an inevitable factor which imparts negative impact on HPA and GBA axis that vibrate our axis leading us prone to inflammatory diseases, vital condition which destroys the equilibrium and increases the susceptibility of infection. Recently when medicinal intervention has shown its limitation nutrition and phytochemicals obtained from vegetables and medicinal plants has gained momentum as a preventive care but more studies needs to be done on its dosage and efficacy effect against diverse population across demographic locations.

Keywords: Nutrition; Cellular Metabolism; Hormones; Normal Microbiota; Immune system; Hypothalamus-Pitutary-Adrenal Axis; Gut-Brain Axis; Stress

List of Abbreviations: -

ATP – Adenosine triphosphate
HPA Axis – Hypothalamus- Pitutary-Adrenal axis
SCFA – Short chain fatty acids
IBD – Irritable/Inflammatory Bowel Disease
SNS – Sympathetic Nervous System
CNS – Central Nervous System
CRH – Corticotropin Releasing Hormone
LC/NE – Locus ceruleus / Norepinephrine
ACTH – Adrenocorticotropic Hormone
ENS – Enteric Nervous System
ANS – Autonomous Nervous System
NAD+ - Nicotiamide adenine dinucleotide
NADP+ - Nicotiamide adenine dinucleotide phosphate
Na – Sodium
K – Potassium
Cl - Chlorine

Introduction

Classification of living organisms is based on shared characteristics like appearance, growth, reproduction, mobility and functionality. All living organisms requires nutrition to perform their metabolic processes in the form of energy which is sourced from food or light like in plants [1]. Unlike plants humans depends on food to full fill its nutritional requirement that helps to determine its appearance, growth, reproduction, mobility and over all wellness.

Extrinsic factor like temperature(37°C) ensures the well ness of living organisms, elevation of which indicates diseased conditions. Intrinsic requirements include source of energy from chemical compounds that are ingested in the form of food and processed by various biochemical reactions that determines its morphological characteristics and excreted as waste in order to keep the circulation of fresh medium. Cell components synthesis requires carbon or its derivative carbon dioxide (in minor quantity) along with gases like nitrogen, sulphur for unification of specific amino acids and proteins. Phosphorus is crucial component for formation of bones and teeth along with trace elements like Iron (Fe), Copper (Cu), Zinc(Z), Calcium (Ca), Magnesium (Mg), Manganese (Mn), Cobalt (Co) etc. are required for enzyme and its cofactor synthesis. Water is fundamental requirement to make the aqueous solutions which aids in transporting nutrients inside the cell. Humans have shared a parasitic symbiotic relationship with normal microbiota that we inherit while passing through birth canal. Microbiome contributes in modulation of biochemical pathways thereby having a significant role in cell physiology. Millennial lifestyle has attributed stress as major extrinsic factor for inflammatory non communicable disease that leads to imbalances of biochemical pathways thereby leading to major chronic diseases. The present article aims to give simplified explanation of how nutrient concentration plays vital role in creating electrochemical gradient which allows the nutrient permeability that ensures our inner equilibrium of HPA axis and GBAaxis.

Role of Potassium, Sodium and Calcium in Cell Physiology

Cell membrane is a phospholipid and protein bilayer structure comprising of hydrophilic heads facing outwards and hydrophobic tails facing inwards (Figure 1)[2].

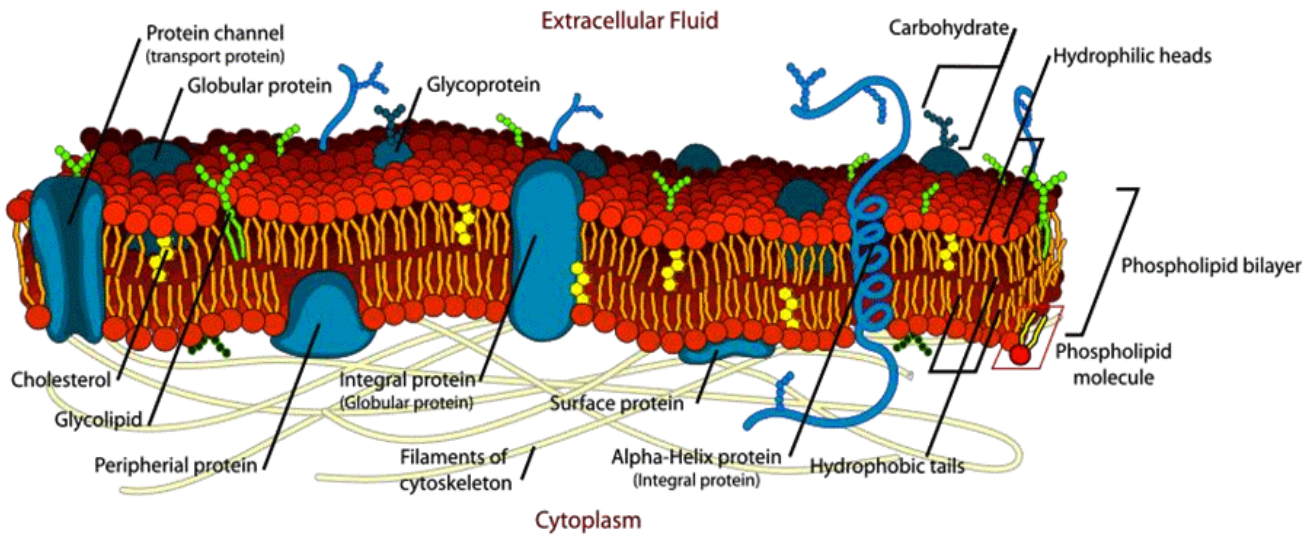

Figure 1: Structure of Cell Membrane [2]

Cholesterol with temperature regulation controls the viscosity of the lipid bilayer. Peripheral proteins adhered by electrostatic force have various functions like signaling, recognition, membrane trafficking, cell division and cell structure. The lipid component of membrane allows high permeability of lipid soluble compounds like steroid, hormones, carbon dioxide and oxygen and restricts passive diffusion of hydrophilic substances. Water, glucose and ions are transported through protein component of the membrane [3]. Transportation occurs with simple diffusion method where energy expenditure is not necessary. Oxygen and Carbon dioxide which are lipid permeable gets transported through passive diffusion however all lipid insoluble compounds like water require to travel into the cell with channel proteins requires energy expenditure thereby creating electrochemical gradient. The factors that contribute to electrochemical gradient generation are 1. Potassium leak channels and 2. Na/K electrogenic Pumps. Later utilizes energy in order to transport three Na ions extracellularly and two K ions intracellularly thereby creating a pool of K intracellularly and Na extracellularly. According to diffusion theory molecules travels from higher concentration to lower concentration which creates a chemical gradient. When electrochemically charged K flows down extracellularly a transmembrane electrical gradient is generated

and theoretically when both electrical and chemical gradients are equivalent ion movement is hindered resulting in resting membrane potential (Figure 2)[2]. Figure represents three states namely 1) resting, 2) activated and 3) inactivated states are highlighted indicating how nerves and muscle cells have ability to transport signals along the nerves and muscle membrane network. Na, K, Cl ions have different permeability but K being high permeable is exerting higher influence in resting membrane condition.

Specific voltage gated channels create action potentials in neurons and muscle cells that interacts with our hypothalamus in the brain which requires Adenosine Triphosphate (ATP). Thus, nutrients like Na, K, Cl plays vital role in brain health which protects our overall emotional and physical wellness.

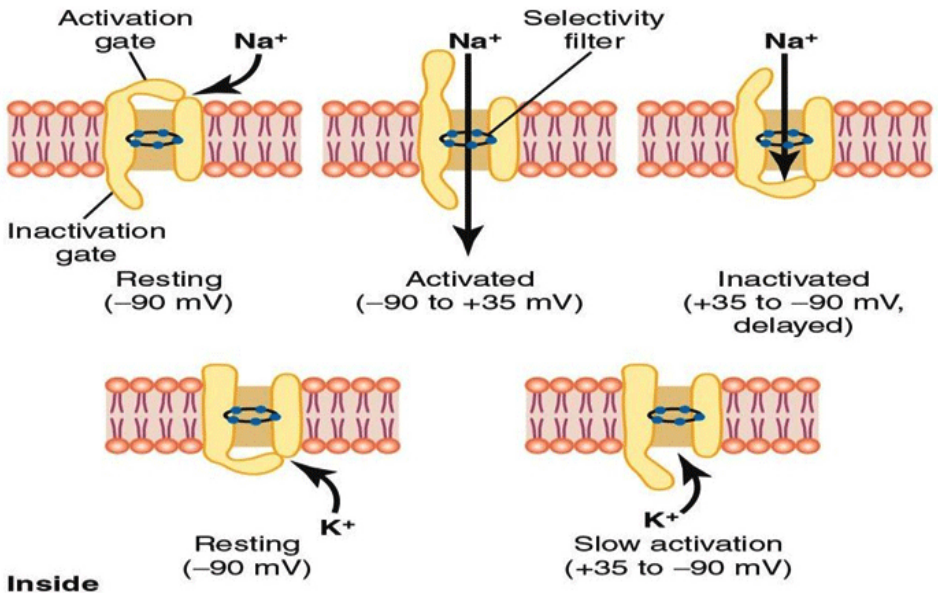

Figure 2: Transport Signals Along the Nerves and Muscle Membrane Network [2]

Bird View of Hormones Affecting Our Wellness

Hormones are peptides/proteins, lipids or amino acid derivatives which after their secretion act on receptors to cause reactions within the respective receptive cells [2,4]. Hormones are chemical messengers that regulate our cell physiology which are consumed in the form of food, drink and air in order to regulate our well being. Interesting characteristics of the hormone is synthesis is a tone place and functionality is at different receptor cell. Alignment of Hypothalamus-Pitutary-Adrenal Axis (HPA axis) and physiologic processes like homeostasis, metabolic demand, development, reproduction are existing due to hormonal processes and secretionrate.

There are three major groups of hormones 1) Proteins and Poly peptide 2) Steroids 3) Derivatives of amino acid Tyrosine. The proteins and polypeptide type include hormones secreted from anterior and posterior of pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland and many more. This group of hormones are stored in secretary vesicles and released when needed. The steroid group of hormones includes the hormones secreted by adrenal cortex (cortisol and aldosterone), the ovaries (estrogen and progesterone), testis (testosterone) and the placenta (Estrogen and Progesterone). This group of hormones are

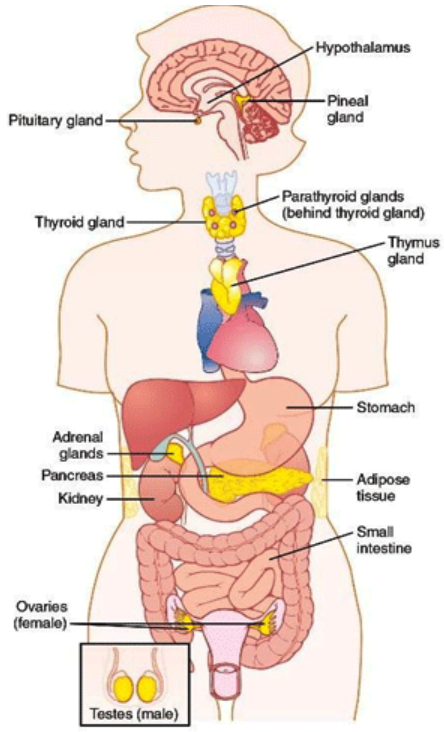

Figure 3: Anatomical View of Hormones synthesis [2]

synthesized by cholesterol and as being lipid soluble hormones, they diffuse across the cell membrane and enter the interstitial fluid to finally in blood [5]. Amine hormones from Tyrosine are secreted by the thyroid gland (thyroxine and triiodothyronine) andadrenal medullae (epinephrine and norepinephrine). This group of hormones is formed by the enzymatic actions in the cytoplasm (Figure 3).

As mentioned earlier hormones have a discrete characteristic of being synthesized in one tissue or gland but functioning or regulating at different tissue or gland [Table1] represents various endocrine glands, hormones and their functions along with chemical structure.

Table 1 Endocrine Glands, Hormones, and Their Functions and Structure

Gland/Tissue	Hormones	Major Functions	Chemical Structure
Hypothalamus	Thyrotropin-releasing hormone (TRH)	Stimulates secretion of thyroid-stimulating hormone (TSH) and prolactin	Peptide
	Corticotropin-releasing hormone (CRH)	Causes release of adrenocorticotropic hormone (ACTH)	Peptide
	Growth hormone–releasing hormone (GHRH)	Causes release of growth hormone	Peptide
	Growth hormone inhibitory hormone (GHIH) (somatostatin)	Inhibits release of growth hormone	Peptide
	Gonadotropin-releasing hormone (GnRH)	Causes release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	
	Dopamine or prolactin-inhibiting factor (PIF)	Inhibits release of prolactin	Amine
Anterior pituitary	Growth hormone	Stimulates protein synthesis and overall growth of most cells and tissues	Peptide
	TSH	Stimulates synthesis and secretion of thyroid hormones (thyroxine and triiodothyronine)	Peptide
	ACTH	Stimulates synthesis and secretion of adrenocortical hormones (cortisol, androgens, and aldosterone)	Peptide
	Prolactin	Promotes development of the female breasts and secretion of milk	Peptide
	FSH	Causes growth of follicles in the ovaries and sperm maturation in Sertoli cells of testes	Peptide
	LH	Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone synthesis in ovaries	Peptide
Posterior pituitary	Antidiuretic hormone (ADH) (also called *vasopressin*)	Increases water reabsorption by the kidneys and causes vasoconstriction and increased blood pressure	Peptide
	Oxytocin	Stimulates milk ejection from breasts and uterine contractions	Peptide
Thyroid	Thyroxine (T_4) and triiodothyronine (T_3)	Increases the rates of chemical reactions in most cells, thus increasing body metabolic rate	Amine
	Calcitonin	Promotes deposition of calcium in the bones and decreases extracellular fluid calcium ion concentration	Peptide
Adrenal cortex	Cortisol	Has multiple metabolic functions for controlling metabolism of proteins, carbohydrates, and fats; also has anti-inflammatory effects	Steroid
	Aldosterone	Increases renal sodium reabsorption, potassium secretion, and hydrogen ion secretion	Steroid
Adrenal medulla	Norepinephrine, epinephrine	Same effects as sympathetic stimulation	Amine
Pancreas	Insulin (β cells)	Promotes glucose entry in many cells, and in this way controls carbohydrate metabolism	Peptide

(Continued)

Table 1 Endocrine Glands, Hormones, and Their Functions and Structure—Cont'd

Gland/Tissue	Hormones	Major Functions	Chemical Structure
	Glucagon (α cells)	Increases synthesis and release of glucose from the liver into the body fluids	Peptide
Parathyroid	Parathyroid hormone (PTH)	Controls serum calcium ion concentration by increasing calcium absorption by the gut and kidneys and releasing calcium from bones	Peptide
Testes	Testosterone	Promotes development of male reproductive system and male secondary sexual characteristics	Steroid
Ovaries	Estrogens	Promotes growth and development of female reproductive system, female breasts, and female secondary sexual characteristics	Steroid
	Progesterone	Stimulates secretion of "uterine milk" by the uterine endometrial glands and promotes development of secretory apparatus of breasts	Steroid
Placenta	Human chorionic gonadotropin (HCG)	Promotes growth of corpus luteum and secretion of estrogens and progesterone by corpus luteum	Peptide
	Human somatomammotropin	Probably helps promote development of some fetal tissues as well as the mother's breasts	Peptide
	Estrogens	See actions of estrogens from ovaries	Steroid
	Progesterone	See actions of progesterone from ovaries	Steroid
Kidney	Renin	Catalyzes conversion of angiotensinogen to angiotensin I (acts as an enzyme)	Peptide
	1,25-Dihydroxycholecalciferol	Increases intestinal absorption of calcium and bone mineralization	Steroid
	Erythropoietin	Increases erythrocyte production	Peptide
Heart	Atrial natriuretic peptide (ANP)	Increases sodium excretion by kidneys, reduces blood pressure	Peptide
Stomach	Gastrin	Stimulates HCl secretion by parietal cells	Peptide
Small intestine	Secretin	Stimulates pancreatic acinar cells to release bicarbonate and water	Peptide
	Cholecystokinin (CCK)	Stimulates gallbladder contraction and release of pancreatic enzymes	Peptide
Adipocytes	Leptin	Inhibits appetite, stimulates thermogenesis	Peptide

Table 1. Endocrine Glands, Hormones and their Functions and Structure [2]

Recently as we see increase in obese population Ghrelin a gastrointestinal hormone released by the stomach and intestine attributes to increase our food intake capabilities, however its exact mechanism in humans still needs to be more studied. Leptin on other hand is known as "Satiety Hormone" produced by adipocytic cells acts against the action of Ghrelin. Dysfunction of leptin ghrelin regulation is one of the factors leading to obesity disease. As variety of foods have different ratio of protein, carbohydrates and fats balance intake must be maintained to regulate the metabolic activities which defines our morphologic appearance. Hence hormones whose concentration in blood is as little as 1 picogram in 1 milliliter of blood and secretion rate being immensely low they play a major role in our wellness quotient [2].

Human Body and Symbiotic association of Normal Microbiota

As we saw human physiology playing extremely vital role on our wellness quotient based on our intrinsic factor diet its extremely important that humans share a symbiotic association with many microorganisms present in the body (Figure 4) [6]

A healthy human fetus is free from bacterial or microbial exposure prior to passing through birth canal where it acquires microbial or bacterial flora through surface contact, inhaling or swallowing them at the time of birth. Depending upon the environmental conditions and physical factors like pH, oxygen availability, nutrient availability for growth they multiply either outside or inside and establish a normal healthy flora making a symbiotic relationship with the host. Each part of body has its specific mixture of microbiota for example nose and nasopharynx has mixture of (S. aureus, S. epidemidis, Branhamellacatarrhalis, Haemophilus influenzae), Oropharynx has mixture of (S. aureus, S. epidermidis, Diptheroids, B. catarrhalis, Haemophillus species, Pneumococci), stomach and duodenum has very few species due to gastric acid creating an unsuitable environment for many bacteria and microorganisms however Intestine Small and Large have highest concentration of bacteria and microorganism especially

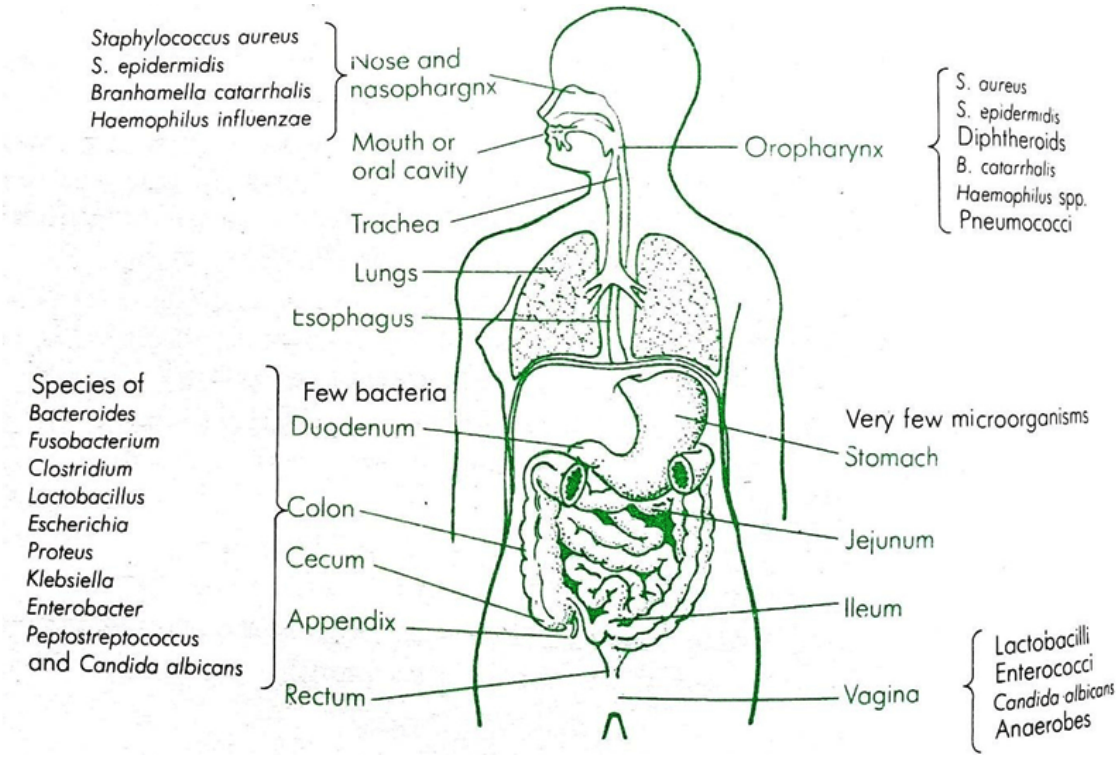

Figure 4: Human Physiology [6]

aerobic and anaerobic microorganisms. The human microbiota mostly the gut microbiome is considered as an "essential organ" [7]. Gut microbiota is involved in many biological processes like modulation of metabolic phenotype, regulation of epithelial lining and defending the pathogenic invasion [8].

Chronic diseases like Irritable/Inflammatory Bowel Diseases (IBD), fatty liver, diabetes has been associated with modulation of gut micro biome. Recently micro biota has been studied to have potential in increasing energy extraction from food, increase nutrient availability and mainly alter appetite signaling. The composition and functionality of the microbiota is differentiated depending upon demographic placements, age, sex, race and diets of the host. Indigested compounds especially the dietary fiber like xyloglucans commonly found in vegetables and other non-digestible fiber like fructo-oligosaccharides and oligosaccharides which contributes to our gastrointestinal health are results of the symbiotic association of the microbiota. The normal microbiota produces 50-100mmol/l perday of Short Chain Fatty Acids (SCFAs) like acetic, propionic and butyric acids that serves as energy source to the host epithelium[9]. Gut commensals have been associated with production of many vitamins like Vitamin K, B vitamins like Biotin, Cobalamin, Folic acid, Niacin, pantothenic acid, Pyridoxine, Riboflavin and Thiamine. Absorption of microbial mediated vitamins takes place in large intestine whereas dietary vitamins are absorbed in small intestine. Alteration in the normal microbiota concentration caused due to strong emotional stress, air pressure fluctuations, starvation, antibiotic treatment, diet, bile acids secretion and antibodies concentration leads to diseased conditions in the host. When host is exposed to some foreign particle the metabolic and physiological requirements of the pathogen determines the severity of the pathogenicity. Naturally resistant host either fails to deliver metabolic factors that are required by the pathogen to flourish or the hosts natural defence system exerts resistance in either cases making a failure to cause diseases.

Stress: A Negative Impact on all Physiological and Metabolic Process

In present condition ample amount of population is engulfed in the deadly clutches of stress which was first coined by scientist Hans Selye in 1936. According to his definition "Stress is a nonspecific response of the body to any demand for change [10]". As we saw the physiology of a cell the physics behind stress comes with the theory of force and resistance. In humans force is physical, emotional or biological that induces our response towards factor causing stress. Selye had designed an experiment in female rats by placing them in various stressful condition and found adrenal hyperactivity, lymphatic atrophy and peptic ulcers [11]. This discovery was an expression of internal environment and linked to Hypothalamus-Pituitary-Adrenal Axis of the body [12]. The HPA axis and Sympathetic Nervous System (SNS) are the peripheral limbs of the stress system [13]. Stress system is activated in Central Nervous System (CNS) and neurotransmitter neurons transport the signals to the entire lymphatic system in the body [14]. The central components of the stress system are Corticotropin Releasing Hormone (CRH) and

Locus Ceruleus -Norepinephrine (LC/NE) autonomic neurons. Behavioural and peripheral changes that ameliorate adjustment towards homeostasis and survival are result of the activated stress system. Cortisol is a glucocorticoid hormone synthesized in adrenal gland once Adrenocorticotropic Hormone (ACTH) binds to the receptor sites. Cortisol primarily acts to increase glucose levels in the body through glucogenesis, lipolysis and proteolysis. It can also increase the appetite, raise blood pressure, decrease bone density and regulation of inflammatory response in normal non stressful conditions. During stressful conditions Cortisol reduces CRH secretion resulting in a decreased HPA axis activity thereby leading to diseases like chronic fatigue, fibromyalgia, hypothyroidism and adrenal depression. The gut commensals have been studied to impart vital role in digestion under stress. Evidence based studies has been done on association of high fat diet and leaky gut increasing intestinal permeability leading to translocation of bacteria [15]. As we saw the correlation between HPA and stress another complex communication network known as Gut Brain Axis (GBA) exists between the gut and Central Nervous System(CNS) which includes Enteric Nervous System(ENS),sympatheticandparasympatheticbranchesofAutonomousNervous System(ANS), neuroendocrine signaling pathways and neuro immune system [16]. Figure 5 represents the communication pathways of the Microbiota-Gut-Brain axisv

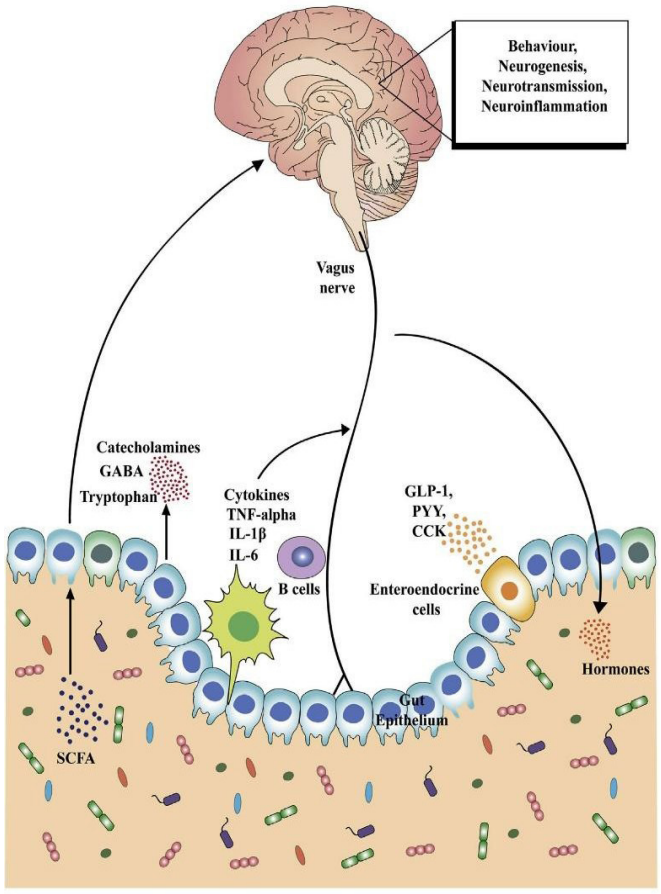

Figure 5: Communication Pathways of The Microbiota-Gut-Brain Axis. [16]

Understanding this complex second communication network detail study of each species of microbiota sharing symbiotic relationship needs to deeply study in order to determine the wellness quotient. Nutrition has been researched to have influence on neurotransmitter and can reverse short term stress conditions [17]. Tyrosine for Norepinephrine (NE) which regulates blood pressure thereby inhibiting hypertension tryptophan for serotonin which affects sleep whose manipulation would cause hyperactive behaviour or insomnia, choline to form acetylcholine that can affect the memory which when manipulated may cause Alzheimer's or dyskinesia, carnitine is essential for brain cells mitochondrial reactions. Vitamins plays vital role of cofactors for fundamental pathways like Krebs cycle, amino acid metabolism. Thiamine (Vit. B1) is well researched to for normal brain functions deficiency in thiamine leads to muscle cramps, neurodegenerative diseases like Alzheimer's, Huntington's and Parkinson's diseases [18]. Niacin(VitB3)deficiency leads to dementia, niacin is precursor of coenzyme NAD+ and NADP+. Pyridoxine (Vitamin B6) deficiency may lead to intractable seizures; cobalamin (Vit.B12) deficiency may cause neurological syndromes and pernicious anaemia. Anaemia highly predominant in women and is associated with diet deficient in folate and enough cobalamin levels. Cognitive dysfunction is a major threat in 21st Century and herbal medicines or medicinal plants have shown to impact the brain health due to the phytochemical constituents present in them without having nutritional role. Some neurochemical molecules are omnipresent in plants and mammalian central nervous system thereby exerting positive health building effect upon consumption. The beneficial effects of phytochemicals are due to their internal antioxidant and anti-inflammatory properties [19].

Conclusion

Nutrition is found to be a vital fuel to initiate all this internal communication and metabolic responses that determines our physiological and morphological make up. The complex reactions modulated by the type of food we ingest, and ingredients combined to prepare the final meal are responsible for our morphological appearance. Nutrients and non-nutritive components of food has become highly potent chemical combustion spark for our hormonal regulation which alters our normal microbiota that determines the intensity of pathogenicity. Recently phytochemicals of medicinal plants and herbs have shown to impart positive preventive care against antibiotic resistant infection sand aid in building our mental health that is destroyed by stress [20]. Stress has been associated with ability of creating inner inflammatory ecosystem leading to devasting health conditions at an early stage of life. A holistic approach with physical activity, nutritious diet and stress management can be the future of preventive healthcare however due to change in lifestyle and preferences its less adaptative. Further studies in the area of phytochemistry could lead to possible cure form vvany non- communicable diseases resulting due to inflammatory ecosystem.

Conflicts of Interest

The author declares no conflict of interest.

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