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A Review on Stress Physiology and Herbal Approaches of Treatment

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ABSTRACT

Stress that is, any type of stimulus that challenges the organism's normal internal balance—induces a physiologic response involving a variety of hormones and other signaling molecules that act on, among other organs, the brain. The most recent research on the relationship between the mind and body involves research in the field of psych neuroendocrinology, which is the study of the relationship between the brain, thoughts and emotions, and the endocrine system. These studies demonstrate a connection between the central nervous system and the endocrine system that were until recently believed to act independently. The autonomic nervous system controls bodily functions which we are largely unaware of and do not consciously control. The part of the autonomic nervous system that is activated during emergencies is the sympathetic nervous system, which speeds up systems needed for survival. The other part of the autonomic nervous system, the parasympathetic nervous system, plays an opposing role. It mediates passive activities and promotes growth and energy storage. Parts of this system are also called into play during stress to slow down systems not required for survival. Ayurvedic literature mentions several herbs exerting favourable influence on brain function in general and memory in particular.

Keywords : Stress, Psych Neuroendocrinology, Ayurvedic, Nervous System, Hypothalamic-Pituitary-Adrenal, CRH, AVP, PVN, ACTH

I. INTRODUCTION

Stress is natural part of life described as experiences that are challenging emotionally and physiologically. It occurs whenever there are significant changes in our lives, whether you and help you become more productive but too much stress response may be harmful[4]. The person·s inability to deals with stress may often lead to clinical dipression[7]. The brain is main organ of body that determines the responce of stress is threatening or not threatening[3]. Stress is the physiological response that is mediated by the stressor to its target organ effect. The three systems human body nervous system, endocrine system and the immune system are directly involved with the physiology of stress[5]. Stress is how a everyone differently and person reacts to stressors. In the 1930s, Selye was an assistant professor attempting to do some research on rats to determine the effects of an ovarian extracts.

He made two observations:

• The body has a set of similar responses to a broad array of stressors.

• Under certain conditions, the stressors will make you sick[8].

Situations that are considered stress provoking are known as stressors[4]. Stress is not always a bad thing. Interactions among the brain, the pituitary gland, and the adrenal glands (i.e., the hypothalamic-pituitary-adrenal [HPA] axis) help regulate the body's response

to stress[1]. The adrenal hormone cortisol plays a key role in stress reduction through its effects on multiple body systems. Excessive cortisol activity during both chronic alcohol administration and withdrawal may underlie some of the clinical complications of alcoholism, including increased risk of infectious diseases; bone, muscle, and reproductive system changes; altered energy metabolism; and disorders of mood and intellect[1].

Stress generally is defined as any stimulus that challenges physiological homeostasis—that is, which alters the balance or equilibrium of the normal physiological state of the organism[33]. When individuals have been continually exposed to st ress for long periods of time (i.e., their stress responses are continuously activated), a situation known as'chro nic stress' can occur[9]. Conventional medicines in Allopathy include some stimulant drugs containing amphetamines and methamphetamine and other popular drugs are Adderall, Ritalin, etc. Most parents of kids suffering kids are concerned about the serious side-effects of these drugs and they should be because these drugs may be permanently altering the brain chemistry of kids and their side-effects like irritability, anxiety, sleep disruption and reduced appetite, sudden tics etc. are worsen the life style of kids[21] . Benson's relaxation response model is now widely used to explain the therapeutic effects of the relaxation response on various health problems. Literature reviews generally concur that all relaxation-response techniques are characterized by reduced stress hormones and reduced central nervous system activity in the form of measurable brain wave changes [12]. Demand for Herbal drugs is ever increasing. Herbal drugs are known to have very minimal adverse effect and its well worth a therapy for chronic CNS diseases like Psychosis which is virtually incurable. India is a country where ayurvada has been practiced from the Vedic ages successfully[34].

II. STRESS PHYSIOLOGY

Importantly, stress evokes adaptive responses that serve to defend the stability of the internal environment and to ensure the survival of the organism[6]. Multiple brain structures are involved in the organization of responses to aversive or stressful stimuli. Among them are the hypothalamus, septo-hippocampal system, amygdala, cingulate and prefrontal cortices, hindbrain regions such as the brainstem catechol- amine cell body groups (A2/C2 cell groups in the nucleus of the tractus solitarius; A1/C1 cell groups in the ventro- lateral medulla; A6 cell groups in the locus coeruleus), the parabrachial nucleus, cuneiform nucleus and dorsal raphe nucleus[12]. When something stressful happens many hormones are released by the brain, nervous system, and other organs . The base of the brain, the hypothalamus secretes an array of hormones into the blood[8]. The hypothalamus – pitutary – adrenal (HPA) axis a major part of neuroendocrine system involving the interaction of the hypothalamus , the pitutary gland and the adrenal gland , is also activated by release of corticotrpin releasing hormone (CRH) and arginine vasopressin (AVP). In response to a stressor , neurons with cell bodies in paraventricular nuclei (PVN) of the hypothalamus secrete CRH and AVP into the hypophysial portal system. These hormones stimulate the pitutary gland to secrete the adrenocorticotropic hormone(ACTH) into the general bloodstream, which results in secretion of cortisol and other glucocorticoids from the adrenal cortex. Substances that promote CRH secretion include (among others) stimulatory neurotransmitters (e.g., glutamate), mediators of inflammation (i.e., cytokines), and CRH itself. CRH secretion is decreased by inhibitory neurotransmitters (e.g., gamma-aminobutyric acid [GABA]); in addition, endogenous opioids provide continuous (i.e., tonic) background inhibition of CRH secretion. There are many chemical messengers that influence secretion of ACTH (by the pituitary) and

cortisol (by the adrenal cortex), only serotonin is shown because of its modulatory effect on multiple brain functions. The stress, such as trauma, infection, intense heat or cold, or mental effort, is followed within minutes by increased secretion of cortisol[11]. The brain also uses cortisol to supress the immune system and reduce inflammation within the body. These corticoids involve the whole body in organism·s response to stress also contribute to the termination of response via inhibitory feedback. Naloxone suppresses inhibition of CRH secretion by opioids; insulin administration lowers blood sugar, activating ACTH and cortisol secretion. The locus ceruleus (LC)/ norepinephrine (NE) system of adrenal medula and pons , also become active and use brain epinephrine to execute autonomic and neuroendocrine responses serving as a global alarm system. The sympathetic nervous system releases epinephrine (adrenaline), and norepinephrine (noradrenaline) into the bloodstream .The autonomic nervous system (ANS) provides the quick response to stress generally called as fight or flight response , involving the sympathetic nervous system (SNS) and withdrawing the parasympathetic nervous system (PSNS) . This results changes in cardiovascular system (CVS) , respiratory system , gastrointestinal system , renal function and endocrine system[10].

III. HORMONES AND NEURORANSMITTERS INFLUENCE THE HUMAN BEHAVIOUR

Neurotransmitters were defined as chemicals that were synthesized in nerve cells, crossing the space between two neurons (a synapse) to act on receptors on the post- synaptic cells. In addition, chemicals also can act as neuromodulators, altering receptor sensitivity, or neurotransmitter availability or action. Behavioral effects for particular hor- mones and neurotransmitters generally are assumed to reflect tissue specific receptors. In the nucleus the hormone-receptor complex is capable of activating genetic transcription, and the sub- sequent production of other compounds, including enzymes and receptors for other mole- cules. Many hormones, especially steroids and peptides, circulate in conjunction with binding proteins. Hormone actions generally depend on the availability of free, i.e. not protein bound, hormone[15].

TABLE 1 - Major Neurotranmitters & Their Neuronal Pathways [2]

S.No.	Neurotransmitter	Neuronal Pathway
1	Norepinephrine (NE) (a major excitatory neurotransmitter)	Locus ceruleus Limbic system, especially Amygdala Hippocampus Septum And interconnecting pathways
2	Serotonin (5-HT)	Postganglionic sympathetic nervous system ,Cerebellum, Brain stem Limbic system
3	Acetylcholine (Ach)	Neuromuscular junctions Preganglionic sympathetic nervous system Preganglionic nervous system parasympathetic nervous system , Postganglionic parasympathetic nervous
4	Gamma amino butyric acid (GABA) (a major	Septal– hippocampal system

	inhibitory neurotransmitter)	
5	Dopamine (DA)	Hippocampus Substantia nigra Limbic system– general Mesolimbic system Nigrostriatal system

DOPAMINE - Dopamine has a key role in a range of neurochemical and neurohormonal functions including cognition, sexual behavior, milk production, coordination and motricity. Dopaminergic neuronal cell bodies originating in the substantia nigra (SN), hypothalamus, ventral tegmental area (VTA), arcuate nucleus . The nigrostriatal pathway originates in the SN and projects to the striatum where it controls the initiation and movement of muscle via the prefrontal cortex. Mesolimbic pathway cell bodies are found in the VTA and terminate in various limbic regions such as the nucleus accumbens (NA) and amygdala, where they are involved in desire and reinforcement behaviors. Mesocortical dopamine fibers originate in the same region but project to the cortex where they mediate emotional and motivational responses. The tuberinfundibular dopamine system has cell bodies in the arcuate nucleus and periventricular region of the hypothalamus where they project to the median eminence to regulate anterior pituitary prolactin secretion. The hypothalamic-derived incertohypothalamic dopamine pathway innervates the dorsal anterior hypothalamus, including the supraoptic nucleus (SON) and paraventricular nucleus (PVN) and the lateral septal nuclei where it is believed to have a role in endocrine regulation and sexual behavior [16]. These findings raise questions about the behavioral contexts in which dopamine would modulate memory formation in the hippocampus, and the implications for episodic memory in humans. Until recently, the role of dopamine in episodic memory in humans has been relatively understudied .If anything , studies with humans with specific impairments of dopamine transmission, such as in Parkinson's disease. Parkinson's disease involves relatively selective depletion of dopamine in the dorsal striatum and thus does not provide a good model for understanding dopamine in the hippocampus[18].

CORTISOL – Cortsol is produced in vivo from cholesterol and is secreted principally from the adrenal cortex. Endogenous cortisol has many known physiological effects including anti-inflammatory, energy regulatory, glucose regulatory,and immunosuppressive effects. The synthetic equivalent of endogenous cortisol is known as hydrocortisone. Glucocorticoids such as prednisone and dexamethasone are also used for these purposes, with increased potency relative to cortisol. Cortisol is the major output hormone of the hypothalamic-pituitary-adrenal (HPA) axis in humans. Cortisol secretion also maintains a regulated circadian rhythm. Activation of the HPA axis beyond the normal circadian rhythm and the subsequent release of cortisol are often associated with stress (Selye, 1985). However, cortisol secretion is not inextricably coupled with the subjective feelings of stress, and subjective feelings of stress do not always translate into high cortisol levels. Thus, high levels of cortisol do not directly cause subjective feelings of stress[17].

Cortisol the stress hormone present in your body all the time, but levels increase in response to danger and stress. In the short-term, its effects are positive, to help you deal with an immediate crisis, but long- term stress means that cortisol builds up and creates a number of stress- related health problems[14].

ADRENALNE - The release of adrenaline causes rapid changes to your blood flow and increases your

breathing and heart rate, to get you ready to defend yourself (fight) or to run away (flight). You become pale, sweat more and your mouth becomes dry.

Your body responds in this way to all types of stress as if it were a physical threat. You may merely be having an argument with someone, but your body may react as though you were facing a wolf. If the threat is physical, you use the effects of the adrenaline appropriately to fight or to run, and when the danger is passed your body recovers. But if the stress is emotional, the effects of adrenaline subside more slowly, and you may go on feeling agitated for a long time. If the causes of stress are are long-term, you may always be tensed up to deal with them and never relaxed. This is very bad for both your physical and your mental health[14].

ACETYLCHOLNE - A neurotransmitter released activated psrasympathetic nervous system that decreases the metabolic activity and returns the body to homeostatis from the stress. The influence of pasympathetic drive is associated with reduction in heart rate, ventilation, muscle tension & several other functions. The parasympathetic nervous system is dominated by the tenth cranial or vagus, nerve which in turn is influenced by brain stem. The parasympathetic drive is responsible for enrgy conservation & relaxation. This is referred to as anabolic functioning during which the body cells are allowed to regenerate[5].

OXYTOCIN - release from axon terminals occurs in the classical manner where axonal terminal release is preceded by an influx of calcium into axonal terminals in response to an invading action potential. Oxytocin can also be released from magnocellular oxytocin neurons in the PVN and SON to regulate its own release. Unlike axonal release of oxytocin, dendritic release of oxytocin is triggered by release of calcium from intracellular stores and is generally electrically independent . Central (axon terminal) and peripheral (via hypophyseal secretion into circulation) oxytocin release from magnocellular cells can act synergistically to influence behavioral consequences. Such synergy between the central and peripheral oxytocin systems does not always exist and there can be an apparent disassociation between the two as seen during a psychosocial stressor 'such as social defeat In the brain, the actions of oxytocin have been shown to be important in coordinating well-defined activities related to socio-sexual behaviors[16].

SEROTONIN – Serotonin (5-hydroxytryptamine or 5-HT) is a mono- amine widely distributed in the brain and involved in mood and impulse control. Dysfunction of serotonergic neurotransmission has been associated with several mood disorders, including depression, anxiety, panic disorder, obsessive compulsive disorder and eating disorder. Serotonergic neurons have a major influence on the regulation of neuro- endocrine function. Serotonergic neurons located in the midbrain raphe innervate the hypothalamus. Many of these neurons also send collaterals to the amygdala and possibly to other limbic forebrain regions. Thus, changes in the serotonergic input to several limbic forebrain regions can be reflected in changes in the serotonergic input into the hypothalamus. Seven families of serotonin receptors have been cloned (5-HT1–7) . Except for 5-HT3 receptors, which are ligand-gated ion channels, all other serotonin receptors are seven transmembrane peptides coupled to G proteins. Evidence supporting a role for serotonin in stress was obtained in microdialysis studies examining changes in extracellular levels of serotonin in different brain areas, including hypothalamus, amygdala, frontal cortex and raphe nuclei, after exposure to several stressors . Insulin injection in fasted rats, exercise and immobilization produce an increase in brain tryptophan availability and serotonin levels in the hypothalamus . Injection of the 5-HT2 receptor

antagonist ketanserin into the amygdala inhibits the effect of photic stress on ACTH release[13].

IV. PLANTS INFLUENCE THE NEUROBEHAVIOURAL ACTIVITY

Traditional medicine involves the use of herbal medicine, animal parts and minerals. Herbal medicines contain an active ingredient, aerial or underground parts of plants as their petal or seeds materials or combinations thereof, whether in the crude state or as plant preparations[24]. The word herb, as used in herbal medicine, also known as botanical medicine or, in Europe, as Phytotherapy or Phytomedicine means a plant or plant part that is used to make medicine to assist the healing process during illness and disease. An herb can be a leaf, a stem, a root, a seed, a fruit, a flower, or bark, used for its medicinal properties. Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care.They are slower acting but have lesser side effect as compare to allopathic medicine. Herbal medicines are divided into mainly three categories. Food herbs (gentile in action lower adverse effect), Medicine herbs (stronger acting dosage and rationale for use) , Poison herbs (strong potential for either acute or chronic toxicity)[25]. According to the WHO about 450 million people in the entire world have suffered mental, neurological, or behavioral problems at some time in their life. Extensive research on plants and their derivatives has taken place in recent years that could provide some new alternative treatments and therapeutic uses for diseases of the central nervous system (CNS)[27]. Indian system of medicine has traditionally been used in several neurological conditions like Alzheimer, Epilepsy, Parkinsonism, and Schizophrenia[28] . Some of the common neurological problems in human beings are Anxiety, Insomnia, Autism, Attention-deficit hyperactivity disorder, Tourette's disorder, Cognition. Antipsychotic drugs like fluoxetine, imipramine and antianxiety drugs like diazepam, alprozolam are used for the many neurological disorders but the drugs producing severe adverse effects and withdrawal symptoms. An herbal medicine overcomes these incidents herbal medicinal plants show same therapeutic effect and lesser adverse effects when compared to modern medicine[23]. Ayurvedic drugs are claimed to act through normal physiological mechanisms. "Mentat" is a herbal preparation containing several herbs like Hydrocotyle asiatica (Brahmi), Acorus calamus (Bachh), Withania somnifera (Ashvagandha), Tinospora cordifolia (Giloe), Evolvulus alsinoides (Shankhpushpi), Nardostachys (Jatamansi) in different doses. The combination of above herbs are processed according to the Ayurvedic principles[19]. Many of the thousands of plant species growing through out the world have a direct pharmacological action on the body .Herbal treatment is a natural form of healing or alternative therapy where herbs and plants are used in the form of extracts, pills, syrup or powder to cure ailments or diseases of human beings and in some cases animals too. Today herbal remedies are back into prominence[20]. Ayurveda includes herbal and nutritional supplementation, meditation, yoga and abhyanga for the treatment of physical and psychological disorder[21].

It may be pointed out that the relationship between depression and anxiety is complex. Both these can coexist in a patient with neurotic illness. In schizophrenia or in organic syndromes, finally depression can be precipitated as a reaction to severe anxiety[22]. Ayurvedic drugs are claimed to act through normal physiological mechanisms. The treatment with "Mentat" produced significant increase in treatment with "Mentat" produced significant increase in GSR (galvanic skin resistance) and decrease in

muscle action potential, indicating relaxation and decrease in sympathetic activity. All the effects might have been independently produced by the several ingredients in the formulation and were complementary in producing a total beneficial effect on memory[19].

TABLE.2 - LIST OF PLANTS USED IN MODIFICATION OF NEUROBEHAVIOURAL ACTIVITY (19,20,21.....31)

S.No.	Plant Name &Family	Common Name	Part Used	Cemical Constituents	CNS Activty
1	Datura metal (Solanaceae)	Datura	Dried whole plant	Tropane Alkaloids – Hyoscamine, Scopolamine	Schizophrenia
2	Rauwolfia serpentina(Apocynaceae)	Sarpgandha	Dried root	Indole alkaloid – Reserpine,Azmaline,Serpentine	Schrizophrenia
3	Azadirachta indica(Maliaceae)	Neem, Margosa	Fresh leaves	Meliacine-Nimbolide,Quercetine	Parkinson's
4	Asparagus racemosus(Liliaceae)	Satavari	Fresh tuber	Asperagin,Shatavarin	Depression
5	Catharanthus roseus(Apocynaceae)	Vinca herb	Dried root	Vincristin, Vinblastin	Alzheimer's
6	Nicotiana tobacum(Solanaceae)	Tobacco	Dried leaves	Alkaloids – Nicotine,Anablastine,Nornicotine	Sedative,hypnoics
7	Centella asiatica(Umbelliferae)	Mandookparni	Dried leaves	Triterpenoids- Asatic acid ,Asiaticoside,Brahmocide,Centic acid	Cognition & oxidative stress
8	Valleriana walichi(Valerianaceae)	Tagar	Dried rhizomes	Valeric acid ,Valerenic acid, Valechlorine,Valerine	ADHD, Stress reliever, hypnotics
9	Bacopa monnieri(Plantaginaceae)	Bhrahmi	Dried leaves	Bhrahmnie, Herpestine, Bacosids,Hersaponin	Cognition, ADHD,memory enhancer
10	Nardostachys jatamansi(Valerianaceae)	Jatamansi	Dried rhizomes	Jatamansone,Nardostachone	Anticonvulsants, Memory enhancer
11	Cryptomeria japonica(Nelumbonaceae)	Japnese cedar, Sugi	Dried inner bark ,seeds	Phytoncide, β-elemol and α-terpineol	Stress relieving, Anxiolytics

12	Nelumbo nucifera(Nelumbonaceae)	Indian lotus	Leaves	Nuciferine,Rosemerine,Nornuciferine	Nootropic,Anxiolytic,Sedative & Hypnotics
13	Canscora decussata (Gentianaceae)	Shankhpushpi	Entire plant and juice	Triterpines,Alkaloids, Xanthones, Glycocides	Anti-anxiety , stress Reliever , Nervine tonic
14	Erythrinia indica(Leguminosae)	Paribhadra	Bark and Leaves	Erythramine,Erysodine,Erysotrine, Apigenine	Anticonvulsants,Anxiolytics
15	Withania smnifera (Solanaceae)	Ashwagandha	Dried root	Alkaloids– Withanine,Somniferinine &Steroids- Withanolides	Anti- stress ,Sedative-hypnotics
16	Rhodiola rosea(Crassulaceae)	Golden root,Rose root	Roots	Rosavin,Rosin,Rosarin,Phenocarbonic Acid	Antidepressant,Insomnia,Lear ning, memory
17	Crocus sativus(Iridaceae)	Saffron Crocus	Stigma, Styletops	Rocrocin,Safranal,Crocetinpic	Antidepressant, Anxiolytic,Sedative
18	Glycyrrhiza glabra (Leguminosae)	Mulethi	Roots, rhizomes	Glycyrrhetinic acid,Glycyrrhizin,Carbenoxolone	Dementia,AnxiolyticAnticon-vulsant,Learning,Memory
19	T Teminalia chebula (Combrataceae)	HhHaritaki	Ripe fruit	tttaTannins – Chebulic acid,Chebulinic acid, Gallic acid, Ellagic acid	M Memory enhancer
20	Panax Ginseng (Araliaceae)	DCPanax(Chinese ginseg)	Dried root	G Glycosides– Panaxadiol,Panaxatriol,Oleanolic acid	D Dementia
21	Cannabis sativa (Cannabinaceae)	Ganja, Bhang	Dried flowering tops and leaves	Cannabidiol, Tetrahydrocannabinol	Anticonvulsant, Sedative
22	Gingko biloba(Gingkoaceae)	Maiden hair Tree	Dried leaves	Gingkolide A,B,C, 4-Hydroxybenzoic acid	Dementia

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