

Basic Principles Of Psychoneuroendocrinology

STUDENT EDUCATIONAL MATERIAL

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Psychoneuroendocrinology is a new approach to six fundamental parts of human medicine which together form it, this branch of medicine combines psychiatry, psychology, neurology, neurobiology, neurosciences, and endocrinology. This new part of medicine focuses on finding answers in the function and dysfunction of the nervous and endocrine system on the change in the psychological status of the patient. It also tries to show how in the same way the psychological dysfunction can affect the bare physiology and cause problems on the nervous and endocrine system. The emerging branch of psychoneuroendocrinology emphasized the importance of exploring the inter-relationships between mind, brain, and hormones¹.

A very good show case of the power of psyche on the neural-endocrine is the phenomena of psychological dwarfism.

Dwarfism is caused by irregular emission of the HGH (human growth hormone) in the system, which in result causes slower growth and irregular height in children. It was discovered that the cause of irregular emission of the HGH in some cases of dwarfism was because of emotional deprivation or unfavorable emotions placed on children. Because of these in general bad conditions for children the psyche started to affect the neural-endocrine which subsequently caused lower emissions of the HGH and the deprived children started to grow in height slower than other children that where the same age but where not in such life conditions. Researchers than took the children which were in unfavorable conditions and placed them in homes where they got all the attention and care they needed, after just a few days the neural-endocrine emission of the HGH started to raise back to normal at a steady and slow rate in a way proving the effect of the psyche on the neural endocrine and the body².

Stress which we already know to have many affects on the human body also can causes problem in neural-endocrine secretion and illnesses which are associated. Although stress is an illness which is accepted and treated in many counties of the world the problem scientists have with it is the perception of stress. Because each individual can experience stress from different things it is hard to find situations in which people have the same amount of stress, it is also important to note not only that the levels of stress can't be measured because of individualism but also that the effect of stress on people varies. Some people who claim that are under stress describe chest pain and edginess while other describe different symptoms¹. Because of this difference between people and their individual responses to stressful situations it is hard to generalize effects of stress to neural-endocrine secretion and find the roots of dysfunction.^{3,4} A complete understanding of the effects of stress on endocrine

functioning not only requires knowledge of the basic neural-endocrine mechanisms regulating the secretion of glucocorticoids via the hypothalamic-pituitary-adrenal (HPA) axis, but importantly requires knowledge of the interaction between this neural-endocrine system and the neurophysiologic evaluative functions that are crucial in experiencing stress.⁵

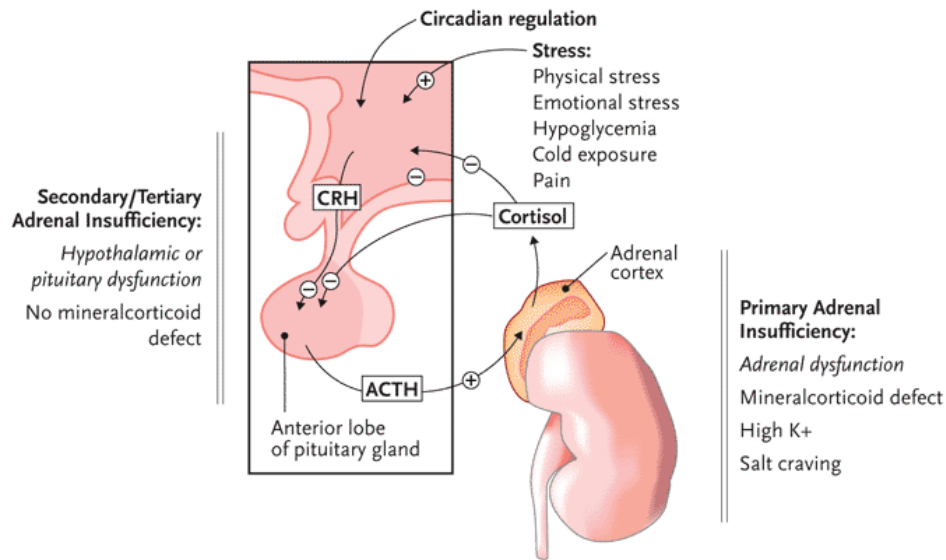
Stress

The term stress or the symptoms that are associated for stress appear in medicine since the 13th century. Over the last 30 to 40 years a considerable empirical basis has been established for the role of cognitive factors for stress in man and animals. Ignoring these results in many claims of relationships between stress, strain, and health are simply not true. Today to define stress we use CATS (cognitive activation theory of stress), which is a more precise and specialized term for the same illness but is not so widely used because it can be rooted to medical information and facts.

History of stress:

Hans Selye is frequently claimed to be the father of the stress concept. However, in his pioneer 1936 paper⁶; a brief note in *Nature*, the term stress was not used. According to tradition, this was because the medical establishment (and the referees in *Nature*) found the term too unspecific, and too much used as a nonscientific attribution concept by the untrained public⁷. In his original 1936 paper, Selye simply described general, non-specific adaptation and maladaptive phenomena in rats exposed to various nocuous agents like cold, surgical injury, spinal shock, or sublethal intoxications. His rats progressed from a general non-specific alarm, through an adaptation phase to maladaptation and death. In his first paper, the syndrome was dramatic with a rapid (6–48 h) decrease of thymus, spleen, lymph glands, liver and fat tissue, erosions in the gastrointestinal tract, edema, loss of muscle tone, fall in body temperature, and changes in the adrenals.

He compared the condition with histamine toxicoses or surgical shock. After 48 h, there was some improvement which he attributed to a shift in pituitary secretion from growth hormone, gonadotropic hormones and prolactin, to thyrotropic and adrenotropic principles. If the treatment continued, the rats would shift from this adaptation stage to maladaptation and death. Stress and stressors appear later in his work. From 1949 or 1950 stress is his main theme⁸. Since he used the term stress on the response rather than the more proper word strain,



he had to invent a word for the load or stimulus that triggered this response. This is the origin of the term stressor⁹.

Hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal axis (HPA or HTPA axis), also known as the limbic–hypothalamic–pituitary–adrenal axis (LHPA axis) is a complex set of influences and feedback interactions among three endocrine glands: the hypothalamus, the pituitary gland, and the suprarenal glands.

When these three organs interact together they form the HPA axis the most important part of neuro-endocrine system which controls the reaction to stress. Besides controlling stress it also controls other major body functions such as: digestion, immune system, emotions and sexuality. The physiological role of the HPA axis and corticosteroids in stress response is so fundamental that analogous systems can be found not only in invertebrates but as well in unicellular organisms as well.

Today we know that a lot of types of stress exist and all of them have an effect on the HPA axis. Stressors can be of many different types—in experimental studies in rats, a distinction is often made between “social stress” and “physical stress”, but both types activate the HPA axis, but through different pathways. The regulation of the HPA axis is done through several neurotransmitters but the most important are: dopamine, noradrenalin, and serotonin. Experiments are also now showing that the neurotransmitter oxytocine, which is associated with positive emotions and social contact have a suppressing effect on the HPA axis causing the stress to be suppressed. HPA axis hormones also certain skin diseases and skin homeostasis. There is evidence shown that the HPA axis hormones can be linked to certain stress related skin diseases and skin tumors. This happens when HPA axis hormones become hyperactive in the brain.

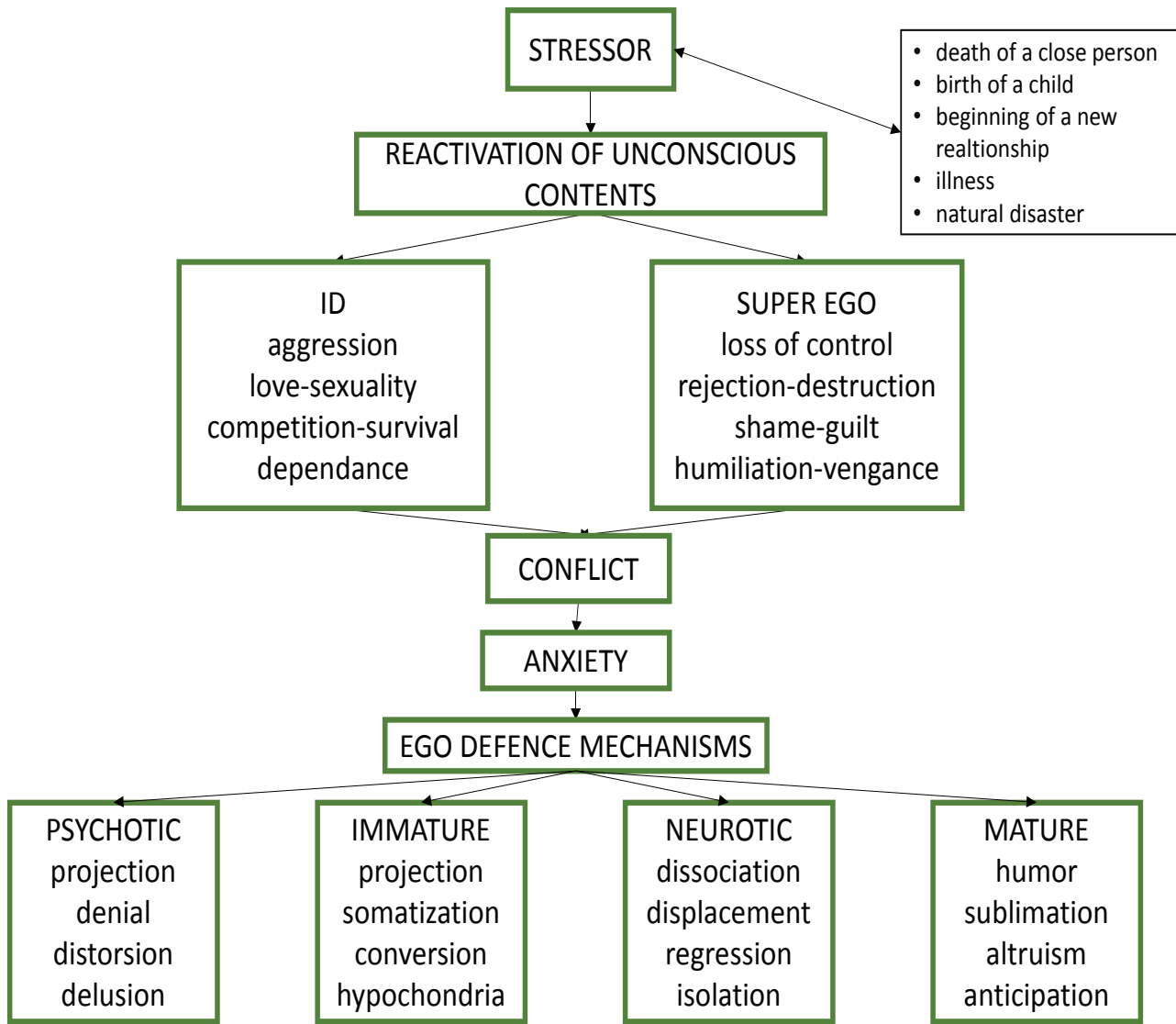
Developmentally-programmed sex differences are also seen in the hippocampus¹⁰. Suppression of dentate gyrus neurogenesis and atrophy of dendrites of hippocampal pyramidal neurons are produced by chronic psychosocial stress, involving the actions of adrenal steroids acting in concert with excitatory amino acid neurotransmitters. As far as we can tell, these changes are reversible as long as stress is terminated after a number of weeks. However, there are also reports that longer duration of psychosocial stress leads to permanent loss of hippocampal pyramidal neurons. In the human hippocampus, MRI studies along with neuropsychological testing have revealed memory impairment and atrophy of the whole human hippocampus in some individuals as they age⁵.

Types of stress and the HPA axis

Prenatal stress (or prenatal maternal stress) is exposure of an expectant mother to distress, which can be caused by stressful life events or by environmental hardships. The resulting changes to the mother’s hormonal and immune system may harm the fetus’s (and after birth, the infant’s) immune function and brain development. This type of stress causes the HPA axis to activate in the mother and in response harming the fetus. After birth babies which were exposed to their mother HPA axis hormones show lower cortisol levels than other children born from mother which had not had such an emotional pregnancy. Low cortisol levels in babies also activate the HPA axis hormones which causes the baby to be in a state which is similar to stress in older age. The mother can shift all her emotions to her child, because of this a happy and fulfilled pregnancy mothers often give birth to healthier and more mental stable children than stressed and unhappy mothers. Mothers which had HPA axis hormones released throughout the pregnancy also have a problem in life after birth; because of the prolonged exposure to the hormones (9 months or less) they require longer time to drop back to normal levels. This type of stress after birth is called prenatal stress. Case studies in which mother reported stress show that their children developed slower and have problems or learn slower how to talk or walk than children from mother who reported no stress and happiness. Also in later life children who were taken care by mothers who had prenatal stress show behavior disorders such as attention deficits, schizophrenia, anxiety and depression; self-reported maternal stress is associated with a higher irritability, emotional and attention problems. All these problems are caused in the child because the mothers HPA axis hormones affected it and in consequence caused the child’s HPA axis to be disrupted and not work properly⁷.

The other type of stress presented is called early life stress. The role of early life stress in programming the HPA axis has been well-studied in animal models. Exposure to mild or moderate stressors early in life has been shown to enhance HPA regulation and promote a lifelong resilience to stress. In contrast, early-life exposure to extreme or prolonged stress can induce a hyper-reactive HPA Axis and may contribute to lifelong vulnerability to stress².

The most widely replicated experiment which show the effect of early life stress is in which rats were subjected to moderate stress levels caused by frequent human handling during the



first two weeks of life had reduced behavioral and hormonal HPA axis mediated stress responses as adults. The other part of this experiments was on done on rats which were subjected to extreme levels of stress in early life and also maternal separation displayed later in life sever stress response and behavioral problems. There are a lot of hypothesi on which way early life stress can affect us for the rest of our life, but the most convincing one is defiantly that in the first weeks of life is stress is every day present and hormones are released through our blood stream our HPA axis gets calibrated or used to such high levels of these hormones and causes lifelong problems because of abnormal calibration. One experiment has shown that, even in the absence of any environmental stressors, early-life exposure to moderate levels of corticosterone was associated with stress resilience in adult rats, whereas exposure to high doses was associated with stress vulnerability.

Though animal models allow for more control of experimental manipulation, the effects of early life stress on HPA axis function in humans has also been studied. One population that is often studied in this type of research is adult victims of childhood abuse. Adult victims of childhood abuse have exhibited increased ACTH concentrations in response to a psychosocial stress task compared to healthy controls and subjects with depression but not childhood abuse.

Heim and colleagues have purposed that early life stress, such as child abuse causes a very high sensation in the HPA axis which in result cause stress induced CRF to be released. If the exposure to

stress is repeated over time the HPA axis get stimulated to hyper secrete CRF from the hypothalamus. Over time, CRF receptors in the anterior pituitary will become down-regulated, producing depression and anxiety symptoms¹¹.

In animal examples it was also shown that maternal care such as licking and grooming causes the suppression of the HPA axis activity. The lower hormone levels caused by lower HPA axis activity and maternal care improve cardiac response, sleep/wake rhythm, and growth hormone secretion in the neonate¹².

Stress and the glucocorticoid receptors

It was mentioned earlier that size of the response of the tissues and cells depended on the sensibility of the glucocorticoid receptor. In an experiment it was demonstrated that when the levels of cortisol where suppressed (lowered) by using dexamethasone the glucocorticoid receptor expressed polymorphism, the participants also had higher body mass index (BMI) and less dense bone structure because of this. From this it can be concluded that the hippocampus, adipose tissue and bone tissue react to cortisol if polymorphism exists in the body. In a broader sense we can expect individual differences concerning the response of specific glucocorticoid receptors. The size of the response those not only depend on the sensitivity of the receptors for cortisol but also on the activity of the whole cortisol signaling pathway which among many things includes enzymes which are responsible for the metabolism of cortisol in the synaptic gap

and other co-activators, compressors etc 13. Variances in all of these segments of the cortisol signaling pathway might have a protective but also harmful effects, it all depends on which receptor they are acting on. In the case of a generalized type of glucocorticoid resistivity we will find that compensatory mechanisms will be activated, like for instance the increase of adrenocorticotrophic hormone (ACTH) and cortisol levels in the serum, but without signs of Cushing's syndrome. HPA axis in these patients is not sensitive on suppression by exogenous glucocorticoids but the regular response to stress is still preserved in this case.

Higher levels of ACTH lead to hyper excretion of androgens from the cortex of the adrenal gland (especially DHEA, DHEA-sulfate, testosterone and delta 4 androstenedione) but also steroids are excreted from the cortex of the adrenal gland in this case such as corticosterone and deoxycorticosterone 14.

Clinical manifestations are different and they vary from asymptomatic states to highly expressed clinical symptoms like chronic fatigue, hypertension with hypokalemia and with or without alka-

losis hyperandrogenemia. In women higher levels of androgen can lead to baldness, formation of acne, irregular menstrual cycle, the loss of ovulation and infertility.

Conclusion

In stress the body undergoes complex endocrine and metabolic changes. Stress is characterized by intensified activity of the HPA axis and the Sympathetic nervous system. Over secretion of cortisol has many negative consequences on the organism which is shown throughout this whole paper.

The sensitivity of glucocorticoid receptors (which depends on genetic polymorphism) and the whole cortisol signaling pathway is responsible for the size of the response of the cell or tissue. Cortisol excretion control, lifestyle change and emotional disorder treatment are all types of intervention which can stop the appearance of unfavorable and potentially dangerous consequences of high cortisol levels on the body.

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