The Non-adaptive Pathologies and Their Neuroendocrine, Mnemic and Clinical Expression

Arnaldo P. G. de Paiva Neto

Graduado em Medicina pela Universidade Federal de Alagoas (UFAL)
Instituição: Faculdade de Medicina (FAMED) / Hospital Universitário Prof. Alberto Antunes (HUPAA)
Maceió / Alagoas, Brasil

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Abstract

The article revises the origin of neurosteroids as production of nervous tissue or "neuroactive steroids" that migrate into the nervous system. Our objective is to explain the adequacy between the neuro-sensory system and the metabolic-motor system. We adopted an explicative research with practical and experimental reports, from hospital observations. This type of analysis attempts to explore the hypothalamic-pituitary-adrenal axis (or HPA axis). There is evidence that bone marrow cells migrate to white matter, hippocampal neurons and cerebral cortex participating in tissue regeneration, primarily linked to memory formation. This formation indicates that the rhythm of the activated brain area is synchronized with the stimuli that excited it. Our whole neuroendocrine system works in sequenced cycles. Any disorder compromises the mnemonic function. There is an inhibitory influence of corticosterone on the expression of PSA-NCAM (which is responsible for the neurogenesis in the hippocampal region). Pregnenolone sulfate reverses aging-related memory deficits in rat studies. The steroid dehydroepiandrosterone (DHEA) inhibits the action of glucocorticoids and makes it possible to ameliorate the immunosuppressive effects of chronic stress. Serum levels of DHEA divided by serum levels of cortisol can be used to correlate with the degree of quality in aging.

Keywords: neurosteroids; hypothalamic-pituitary-adrenal axis; neurogenesis.

Introduction

Logical connections arise to solve problems that were judged as indecipherable. Synaptic plasticity amplifies circuits of the machinery of the brain. When strengthening such neural networks, injury to a dominant brain lobe can be compensated for by training that enables the use of the non-dominant region (which begins to exert greater dominance). Ma (1995) questions whether patient adaptation mechanisms involve only neuroplasticity, because structural regeneration of nervous tissue has not yet become responsible for much of the central nervous system (or CNS) rehabilitation. Recovery is associated with the cognitive and memory functions that require the development of brain areas less activated by disuse. Ribot's Law (1881) points out that recent memories are lost first. Long after that, damage occurs in remote memories. According to Arnaldo Paiva Neto (2019), such law is excepted in cases such as anterograde amnesia in temporal lobe epilepsy, in which the hyperexcitability generated in this lobe impedes the memorization capacity due to the destabilization of the rhythm in relation to the rest of the sequential processing related to the site affected (De Paiva Neto, 2019). One patient suffers a trauma and from that moment we call the memories that preceded the accident by the term "retrograde memory". And we call the new memories that have occurred since that moment by the term "anterograde memory". One of the explanations for retrograde amnesia is the change in the release of hormones from the hypothalamic-pituitary-adrenal axis or HPA axis. Glucocorticoid and mineralocorticoid hormones would act by blocking the processing of autobiographical memory (Piefce, 2003; McEwen, 2000). In this same patient, we will also consider if there was brain damage, which would cause anterograde amnesia due to injury in regions such as the hippocampus and areas of the medial temporal lobe.

The memory imprinted on the brain tissue is represented by the neuromuscular pathway that repeats automatically. This phenomenon of "impression at the cellular level" is known as engrain, fundamental to associate with the physical correspondence of memories. We have proteins that activate or repress the formation of RNA from the DNA template. These molecules bind to the enzyme RNA polymerase that adheres to the site of the DNA that is called "promoter". There are sites of binding with the enzyme that makes it possible to increase or not the manifestation of genes; this is how genes are "activated" or "deactivated" in our body. Different transcription factors are arranged in specific combinations necessary to activate a particular gene. This mechanism is known as "combinatorial regulation" and it is in this way that characteristics are expressed in varying degrees of manifestation. Our body may appear heterogeneous as a mosaic in

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which each physiological system represents the cellular metabolism differently from each other. However, we perceive the individual physical manifestations in a sequenced and relatively synchronous manner at certain intervals of time and space. The flexibility of the DNA structure allows for several sites where the expression of genes in certain cell types is intensified or silenced and according to transcription factors specific to the tissue in question. For example, mutations in the silencers of a coding sequence may result in non-survival of an embryo that has undergone such changes. Faced with the same evolutionary perspective, mutations at the potentiating sites (of another coding sequence) could only slightly change the expression of the affected gene, leading the individual to develop a new characteristic.

Methodology

We adopted an explicative research with practical and experimental reports, from hospital observations of the clinic to the surgery. This type of research is concerned with identifying the factors that determine the spectrum of what we conceptualized as “non-adaptive diseases”. That is, this type of research attempts to explore the hypothalamic-pituitary-adrenal axis (or HPA axis) in relation to the organic function of adequacy between the neuro-sensory system and the motor-metabolic system (which are concepts of Anthroposophy). Our conventional medicine combined with the alternative medical sciences allow broader results about therapeutic plurality. We also use descriptive studies, since the identification of factors that determine a phenomenon requires a certain degree of detail. The research allows subsidies for practical interventions with the objective of solving patients’ symptoms in response to stress (which favor the emergence of digestive, metabolic and neurological problems). It is necessary to review the cholesterol biosynthesis process to explore hypotheses about the so-called “neurosteroids”. Often, patients complain of mnemonic alteration, dysautonomia, dizziness due to dyslipidemia, akathisia and other complaints. To reach the objective of the article that is to explain the adequacy between the neuro-sensory system and the metabolic-motor system, we need to review the concept of neurosteroids. Based on the studies of Tsigos (2002), we divided the non-adaptive diseases into two large groups: the first set of pathologies refers to hyperactivation of the HPA axis. The second group is characterized by hypoactivation of the HPA axis. Another well-discussed subject is about the hormone DHEA (dehydroepiandrosterone). Is there a possibility of aging reversal and neuronal regeneration?

Discussion

The hypothalamus produces thyrotropin-releasing hormone (TRH) which stimulates the adenohypophysis to produce the thyrotrophic hormone or thyroid stimulating hormone (TSH). Serum TSH levels (0.3–4.0 mU/L) and free T4 (0.7–1.8 ng/dL) are normally maintained within the ranges considered during the circadian cycle. Variations in the dosages of these hormones are considered normal, if they remain below 5% in relation to their mean reference values. Anagolously to cortisol, peak serum levels of thyroid hormones decline at night, rising gradually in the late morning to peak values between morning and afternoon, when it returns to decline near sleep. We consider that serum concentrations of melatonin are inversely proportional to this described behavior. We conceived a simplified model of the normal process of regulation of thyroid hormones, in which euthyroid patients express concentrations of each of the main substances involved, within temporal variations and the sleep-wake cycle. Our body tries to adapt to the duration of the clear period (day) and the dark period (night). However, sound, light and environmental information confuse the sense of perception. The suprachiasmatic nucleus (or SCN) perceives light and influences the expression of genes related to the variations of the luminous stimuli. Our body temperature decreases at dawn and increases upon waking in a 24-hour cycle or otherwise known as “circadian cycle” (Martins and Monteiro, 2007). According to our practical experience, some patients with Graves’ disease are able to engage in activities so exhaustively that fatigue prevents the insomnia symptom from manifesting, since it is a pathology that speeds up the metabolic process.

Insomnia seems to occur more commonly in patients who are idle. Although weight loss is clinically important in thinking about changing or maintaining drug therapy, we know that the hypothalamic-pituitary-thyroid axis (or HHT axis) is also linked to adrenal and neurological functioning. Schussler (2000) states that free T4 exhibits a very small variation in the body and this hormone is converted to triiodothyronine (T3): a free hormone that is biologically active. In addition, various changes in carrier proteins (acquired or inherited) alter the serum concentrations of T4 and T3. However, this variation remains minimal and within normal limits for healthy or “euthyroid” individuals (Stockigt, 2001). TSH measurement is the most useful test in the initial evaluation of thyroid function. Although thyrotropin production is altered, there may be only one disease without symptoms and going unnoticed or subclinical. This type of disease is related to metabolic disorders that can de-structure the adaptive capacity (if the patient develops symptoms), since the accelerated or slow metabolism makes it difficult for the body to react to the new information of the environment and to respond to the new sensorial stimuli (light, sounds, smell, taste and textures). There are risk groups such as pregnant women with autoimmune diseases (e.g. type 1 diabetes mellitus, vitiligo, pernicious anemia, primary adrenal insufficienty and others), users of medications (e.g. lithium, cytokines, amidarone), hypercholesterolemia, hyponatremia, anemia, presence of comorbidities such as sleep apnea, depression or dementia. Thyroid stimulating hormone, prolactin, aldosterone, renin, testosterone and corticosteroids are related to the existence of circadian rhythmicity (De Almondes and De Araújo, 2003).

Van Gool and Mirnirian (1986) argue that there is fragmentation of the sleep/wake cycle in the elderly, taking into account their habits throughout life. Irregular hours of work, leisure and meals make restful sleep difficult. The spectrum of organic changes (in an attempt to adapt) decreases the immune system (through high levels of cortisol). We know that there is REM sleep (i.e. sleep in which “rapid eye movement” occurs, accompanied by more vivid dreams). Pace-Schott (2002) describes that there is an intermediate element in the transition process between REM sleep and wakefulness. Waking up would be a state with a lot of release of amines (which are substances like dopamine, serotonin, melatonin, epinephrine and norepinephrine), that is, a predominantly aminergic state occurs. During REM sleep there would be receptor binding that recognizes acetylcholine as muscarinic, i.e., REM sleep would be a predominantly muscarinic cholinergic state. Brain areas interact with each other. We understand that during the transition between sleeping and waking, the brain may have some difficulty interpreting whether it is dreaming or not. The intermediate state corresponds to sleep in which the rapid movement of the eyes does not occur (also known as “NREM” sleep). In the face of doubt about whether we are awake or not, we can respond calmly to this.

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questioning. But we can also feel this awakening with fight or flight reaction, associated with greater releases of cortisol. As cortisol is also released in a tranquil wake-up process, we may think that the release of endorphins helps in the interpretation that makes the circadian cycle pleasurable. Well-being is something that also involves memories.

Among the adaptogenic remedies, we selected the medication called "ashwagandha" which reduces cortisol levels by 25%. The treatment group that was given ashwagandha exhibited a significant reduction (p<0.0001) in scores on all the stress-assessment scales, relative to the placebo group. The serum cortisol levels were substantially reduced (p=0.0006) in the ashwagandha group, relative to the placebo group (Chandrasekhar; Kapoor; Anishetty, 2012). One medication that has become popular is the hormone DHEA (dehydroepiandrosterone) that is related to the reversion of aging, anticancer effects and glycemic control (Chopra, 1994). This substance that is becoming popular arises from the metabolism of 17-OH-pregnenolone and is converted into sex hormones (androgens and estrogens) in peripheral tissues (such as gonads). There is the concept of a DHEA "reservoir" that we are provided at birth. Every time our body produces adrenaline and cortisol, we use a little of that deposit. Arnaldo Paiva Neto (2019) argues that there is a relationship represented by the division of values of: "serum levels of DHEA / serum levels of cortisol". Such division can be used in geriatric follow-up and to correlate with the degree of quality in aging (De Paiva Neto, 2019). So, the increase of DHEA and the reduction of cortisol manifests positively in individuals who maintain a long quality of life, meditation and non-concern. Blood flow tends to increase from the first minute of stress. Vitamin C contributed to improve this flow in eutrophic children and obese children (Fernandes, 2011).

Chronic stress leads to changes in the cardiac sympatho-vagal balance. When we characterize the sympathetic nervous system (SNS), we refer to adrenaline symptoms (e.g. increased blood pressure, sweating, bronchial dilatation, decreased large bowel motility, increased heart rate and respiratory rate). Some of our patients have been taking beta-blockers, precisely to control such an exacerbated action of the SNS. And the metabolic syndrome itself is associated with sympathetic hyperactivation and reduced baroreflex sensitivity (Schlaich, 2015). In the pathophysiology of obesity and heart disease, the peripheral vasodilator response is impaired and blood flow becomes impaired. Studies have shown that treatment with antioxidants (e.g. vitamin C at high doses) increases the production of nitric oxide or activates the action of antioxidants, restoring endothelial function in patients with increased peripheral vascular resistance. High doses of vitamin C would act as a priority reducing superoxide anions, while their chronic oral therapy increase nitric oxide production and activate the action of antioxidants, restoring endothelial function in obese individuals (Fernandes, 2011). Baulieu and Robel (1998) may explain the possibility of nerve tissue producing steroids de novo, that is, autonomously in relation to the production of peripheral glands (originating the so-called "neurosteroids"). Regardless of where they are produced, CNS-acting hormones are conceptualized as "neuroactive steroids" that can modify the encephalic structure of adaptation to environmental stimuli.

The hippocampal administration of the neurosteroid "pregnenolone sulfate" (abbreviated as PregS) reverses aging-related memory deficits in rat studies (Vallée et al., 1997). Regarding the human brain, Lanthier and Patwardhan (1986) performed studies of patients after dying (or postmortem), and found that pregnenolone is the most abundant neurosteroid in brain tissue, followed by DHEA as the second more abundant. Mayo et al. (2005) concluded that PregS enhances neurogenesis through the expression of PSA-NCAM (meaning "polysialylated neuronal cell adhesion molecule"). Paradoxically, there is a positive gamma-aminobutyric acid receptor modulator (known as the GABA receptor). And this modulator is called "allopregnanolone" or AlloP that produces an effect opposite to the mechanism of action of PregS, reducing hippocampal neurogenesis. However, AlloP favors the effects of progesterone on cognitive and morphological recovery, with decreased neuronal death (He, Hoffman and Stein, 2004). The explanation comes from the fact that allopregnanolone reduces the expression of pro-apoptotic proteins, influencing the formation of glial scars and allowing better cognitive performance (Djebali et al., 2005). There is an inhibitory influence of corticosterone on the expression of PSA-NCAM. Melancholic depression has been described as deregulation of negative feedback in the hypothalamic-pituitary-adrenal axis (or HPA axis), associated with hypercortisolemia (Pariente and Miller, 2001).

Patients complain of obesity, skin changes (e.g. hirsutism, striations in the abdomen and thigh), fatigue, bone loss, high blood pressure, menstrual irregularity, hyperglycemia and emotional unrest. We think of Cushing's syndrome, another hypothesis may be metabolic syndrome, polycystic ovary syndrome and we also question hypothyroidism. Some patients may be given 2 mg of dexamethasone every 6 hours for 48 hours or to take 8 mg of dexamethasone between the hours of 23 h and 24 h with the need to dose plasma cortisol the next day. The dexamethasone suppression test (or TSD) is based on this described procedure and was performed in severe depressed patients with surprising results: cortisol levels remain high and have no suppressive effect in response to dexamethasone use. In Cushing's syndrome, these described tests cause more than 50% reduction of ACTH secretion and, therefore, reduction of cortisol. In Cushing's syndrome, these tests described cause more than 50% reduction of ACTH secretion and, consequently, reduction of cortisol. In extrahypophysal tumors the ectopic secretion of ACTH remains high. Some occult carcinoid tumors may exhibit suppression of ACTH levels, mimicking Cushing's disease. However, blood tests from the same patients demonstrate that ACTH dosage is decreased after corticotrophin releasing-hormone injection (or HLC injection). The most striking is that previous treatment with dexamethasone enables the increase of ACTH secretion after HLC injection. Therefore, some scientists choose to request the dexamethasone suppression test along with the HLC stimulation test. There is the low-dose dexamethasone test (1 mg) and, together with the 24-hour urinary cortisol dosage, are the most practical tests for diagnosis of Cushing's Syndrome (Castro and Moreira, 2002).

According to Tsigos (2002), some disorders may occur with hyperactivity of the HPA axis, including anorexia nervosa, obsessive-compulsive disorder, panic, chronic alcoholism, alcohol or narcotic withdrawal, diabetes mellitus and hyperthyroidism. In our conduct, we requested TSH, free T4, fasting glycemia, glycated hemoglobin, lipogram, electrolytes, electrocardiogram, serum basal cortisol, ACTH, vitamin D, bone densitometry, pelvic ultrasound and others depending on the results and follow up of the case. We classify whether hypercortisolism is ACTH dependent or ACTH independent. The ACTH dependent includes: pituitary adenoma, pituitary carcinoma, pheochromocytoma, medullary thyroid cancer, small cell lung cancer, or prostate cancer. The ACTH independent includes: adrenal adenoma, adrenal cancer, McCune-Albright syndrome, neuroblastoma or Wilms tumor.
Pasquali et al. (1993) demonstrated that in women (with central obesity) there was an increased plasma cortisol response when they underwent HLC or ACTH stimulation. Women with peripheral fat deposition showed a lower cortisol response than the control group. Metabolic syndrome manifests itself in the same individual through dyslipidemia, type 2 diabetes mellitus or glucose intolerance, hypertension and overweight. Evidence indicates that CRH and neuropeptide Y stimulate the NHS through insulinemia, the determination of insulin resistance by vasoconstriction in the vascular bed of skeletal muscles, the activation of descending pathways from the hypothalamus to the spinal cord and sympathetic neurons (Matos; Moreira and Guedes, 2003).

There is also the group (of diseases) that is characterized by hypoactivation of the HPA axis. In which the secretion of corticotropic releasing hormone (HLC) is decreased. This situation occurs in patients with posttraumatic stress disorder, seasonal depression, atypical depression, chronic fatigue syndrome, hypothyroidism and fibromyalgia. Laboratorially, urinary excretion of free cortisol is decreased. Clinically, the complaints are of fatigue, indisposition, muscle aches, dry skin, nail thinning, less hair, constipation, weight gain, swelling and slowness. In these cases, 5 mg prednisolone and salivary cortisol evaluation indicate poor glucocorticoid rates. Concentrations of HLC in cerebrospinal fluid may be decreased (the opposite of what occurs in HPA axis hyperactivity). The frontal cortex tends to have a higher number of corticotropin releasing hormone receptors. Some studies have aimed to relate this hormone to decreased libido and appetite, also influencing psychomotor alterations and sleep disturbances (Jurueña, Cleare and Pariante, 2004). Regardless of the relationship between Cushing's Syndrome and psychiatric diseases, it is essential to understand that the adaptation process involves the neuroendocrine system and there is no way to separate the “spectrum” or “interval” that encompasses pathologies aggravated by stressors. Infrastructural rhythms present superior duration to the circadian rhythm, that is, the cycle of the infradian rhythm occurs in 28 hours, which are 4 hours longer in relation to the circadian cycle. And the ultradian rhythm is just the opposite (Silveira et al., 2012).

The functioning of the endocrine system is closely related to the rhythmicity of chronobiology. The hormone secretion provides examples for all types of rhythms. Each presents its circulating hormone peak of maximum production and secretion at different times of day according to the typical needs of each species. Hormone secretion provides examples for all types of rhythms. Each presents its circulating peak of maximum production and secretion at different times of the day. For various hormonal secretions such as thyrotropin, prolactin, aldosterone, renin, testosterone and corticosteroids are visible to the existence of circadian rhythmicity. Through the administration of potassium iodide, short-term iodine overload may cause an increase in thyroid hormones (by the effect called “Jod-Basedow”) or block in thyroid function (by the effect called “Wolf-Chaikoff”), with consequent hypothyroidism (Woeber, 1991). Endocrine syndromes clearly have a close relationship with our suitability between the nervous-sensory system and the metabolic-motor system. There is a rhythmicity of the production of glandular secretions (in general) combined with smooth muscle motility to preserve homeostasis (Lanz, 1988). In addition, we can not forget irritable bowel syndrome, where our emotions may interfere with altered motility or spasm of the intestinal musculature and alterations in digestive secretion (Ribeiro et al., 2011).

Arnaldo Paiva Neto (2019) classified the types of amnesia into two major groups: in the first set, organic causes prevailed, and in the second, psychological causes prevailed. In practice, our minds work by action of both etiological groups, with different degrees of influence. The organic causes are divided into two subgroups. One of the subgroups represents structural causes (vascular, trauma, ischemic, neoplastic, chronic infectious, severe traumatic brain injury or severe TBI and other origins that damage engrams formed in a certain location in the central nervous system or CNS). The other subgroup represents organic causes due to lack of memory consolidation (e.g. sleep disturbances, lack of memory exercises, malnutrition or deficiency states, depression, acute confusional states or delirium, convulsions, acute infections or encephalitis, mild traumatic brain injury (or TBI) and other insufficiently stimulating conditions for memory consolidation. There is also a relationship with the aging process that leads to decreased vision and space skills (De Paiva Neto, 2019). When it comes to an emotionally unbearable memory, mechanisms of repression and oblivion occur. We emphasize the famous Freudian phrase that affirms about moments in the life of the people in which the words lose the sense and, however much we think of a way of employing them, they do not seem to serve. So we do not say. We deal with the origins of trauma and the psychological memory is exemplified in this context.

We know that in medical practice the origins of forgetfulness are commonly associated with organic and psychological reasons. Among the reversible dementias, their cause may be secondary to a stroke, ischemic microangiopathies, depression, hypothyroidism, vitamin B12 deficiency (after bariatric surgery, atrophic gastritis or intestinal inflammation), infections (by neurosyphilis or HIV), aluminum poisoning, drugs (illicit or even licit, such as benzodiazepines, example “clonazepam”), normal pressure hydrocephalus (with symptoms of dementia, apraxia and urinary incontinence). While primary dementias result from Alzheimer's disease, Lewy body disease, parkinsonism, frontotemporal disease (early atrophy and neuronal loss). Albert and Urrahy (1997) made a list of the physical manifestations that are most commonly found in daily life, with chronic stress as risk factors for myocardial infarction, arrhythmias, arterial hypertension, atherosclerosis, hemorrhagic or ischemic stroke, ulcers, gastritis, inflammation, colitis, chronic diarrhea, premature aging, skin rash, urtiical lesions, hair loss, psoriasis, mycosis, impotence and frigidity, osteoporosis and decreased immunity caused by circulating cortisol levels. The nervous system is associated with the glands that need to be in sync with biological clocks (which are the cycle of temperature, pressure, metabolism, and other biological needs at a particular time of day). In medicine, we use the term “dissociation” in several senses. If we consider it as "loss of body rhythm," we understand that it can be applied in cardiology, endocrinology, neurology, psychiatry, and so on.

Synchronization occurs between an area of the brain interacting with the external environment. We use the term "category 1" to refer to this mechanism of synchrony of the nervous system with the external environment. For example, disturbances affecting the described category are observed in patients who report irregular sleep because they require an environment with less light and less noise. There is also synchronization between distinct brain regions that interact, acting together with certain physiological functions. We use the term "category 2" in the classification of synchrony mechanisms. For example in focal epilepsy in which a site of the brain has an electric discharge more intense than normal and that makes its activity much more differentiated than in other areas. The
pathological mechanism refers to “marked loss of synchrony between brain areas.” Category 2 can lead to memory dysfunction (De Paiva Neto, 2019). We call the term “category 3” referring to the hormonal variations by function of the glands that interact with the nervous system. If only we could get hungry, thirsty and other biological needs at the most appropriate time. It would be perfect if people could always sleep well (with all the functions preserved).

However, the daily stress represented by cortisol peaks sabotages our ideal functioning. We are forced to adapt. Adaptation occurs by neuroplasticity and there are some places where regeneration facilitates the process. Neuromodulation stimulates the nervous system to change in response to external stimuli.

If we compare feelings with the layers of an onion that we peeled, we have in the center the psychic pain (represented by the ideas: “I feel alone”, “I want to be respected” and “I want to be recognized”). There is the memory of the mother’s lap as a way to protect oneself from the anguish of separation. From there, the feeling of being strong (what they call primary narcissism and which is the fantasy represented by the thought: ‘I have everything at the time I need” or “I cry and I am treated”). The primary gain is attention, since we need it and this is absolutely human and necessary. Faced with frustrations and failures, two myths represent our sense of “life is good” or “life is bad.” These perceptions are best exemplified by the idea of the Phoenix myth that points out that it is worth reviving. In response to this stage of thoughts, secondary narcissism arises which may come as “I make myself happy.” The big question is to find out what makes people happy. Consciousness is the window through which the inner light is externalized, being the vehicle of intelligence. Dissociation is an event that relates to the disconnection that some people suffer between their memories and their own identity. Hormone production is influenced by the phenomena of stress, dissociation, emotion, and life habits. Non-adaptive diseases can be confused with other disorders. Aleixo (2016) states that extrapyramidal symptoms may be medication side effects (such as akathisia, dystonia, pseudoparkisation or dyskinesia).

For us to understand non-adaptive diseases, we need to separate groups of patients as the production of sex hormones decreases. Menopause occurs between the ages of 45 and 55. Andropause occurs between 40 and 55 years. We have characterized that younger patients predominantly present cases of acute stress. In contrast, older patients report routine cases of chronic stress. Acute stress is related to tension headache, muscle aches, heartburn, flatulence, diarrhea, heart palpitations, increased blood pressure, sweating, and other symptoms. Acute episodic stress can aggravate headaches and muscle aches that become persistent. Chronic stress is more related to fatigue, exhaustion, hypervigilance, insomnia, heart disease, discouragement, sadness, immunosuppression, metabolic syndrome, depression and other complications.

Conclusion

The steroid dehydroepiandrosterone (DHEA) inhibits the action of glucocorticoids and makes it possible to ameliorate the immunosuppressive effects of chronic stress (Pagliarone and Sforzin, 2009). There is a relationship between “serum levels of DHEA / serum cortisol levels” that can be used in geriatric follow-up and to correlate with the degree of quality in aging. The prognosis is better the higher the values of natural numbers of this relationship, except in severe or dysfunctional cases and hypocortisolism. We propose to classify non-adaptive diseases in two groups. In the first group, there is a hyperactivation of the HPA axis associated with states of: severe chronic disease, anorexia nervosa, melancholic depression, obsessive-compulsive disorder, panic disorder, malnutrition, diabetes mellitus, hyperthyroidism, central obesity, chronic excessive exercise, childhood maltreatment and pregnancy. In relation to the second group, we divided the hypoactivation of the HPA axis associated to the following states: atypical depression, chronic fatigue syndrome, seasonal depression, fibromyalgia, hypothryoidism chronic, posttraumatic stress disorder, post glucocorticoid therapy, nicotine withdrawal, adrenal suppression, rheumatoid arthritis, postpartum and menopause. Acute stress is related to tension headache, muscle aches, heartburn, flatulence, diarrhea, heart palpitations, increased blood pressure, sweating, and other symptoms. Chronic stress is more related to fatigue, exhaustion, hypervigilance, insomnia, heart disease, discouragement, sadness, immunosuppression, metabolic syndrome, depression and other complications.

In the classification of synchrony mechanisms, we call the term “category 3” referring to the hormonal variations by function of the glands that interact with the nervous system. The daily stress represented by cortisol peaks sabotages our ideal functioning. Faced with constant changes in cortisol levels, we consider adaptogenic medications that revert the aging process and apoptosis. From the vascular point of view, the use of acetylcholine, beta blockers and calcium channel antagonists stand out. Some scientists have studied revolutionary pathways of pharmacological action. We call these pathways a “21st-century tripod”: based on “neurosteroids,” “neurogesenes,” and “anti-tumor,” as example ixolaris that blocks primary tumor growth and glioblastoma angiogenesis (still in the studies). We summarize in the topics below the conclusions that we obtained after the whole research:

1. There is an inhibitory influence of corticosterone on the expression of PSA-NCAM;
2. PregS enhances neurogenesis through the expression of PSA-NCAM;
3. AlloP produces an effect opposite the mechanism of action of PregS, reducing hippocampal neurogenesis. However, AlloP favors the effects of on cognitive and morphological recovery, with decreased neuronal death (after traumatic brain injury).
4. There is evidence that bone marrow cells migrate to white matter, hippocampal neurons and cerebral cortex participating in tissue regeneration, primarily linked to memory formation (Mezey, 2003);
5. PSA-NCAM expression and neurogenesis occur in the hippocampal region.

According to Claudia Rother and Jutta Oexle (2010), 43 doctors met with about seven patients for each physician. The number of patients totaled 300 individuals, being 234 women and 66 men.
The youngest patient was 7 years old and the oldest patient was 94 years old. The majority of patients declared themselves to be economically active (with an average age of 50 years). From the admission consultation there were symptoms to be evaluated prospectively (in the total period between December 2008 and August 2009). About two-thirds of the patients used active homeopathic principles. About 14.2% of the patients took beta-blockers. Other drugs (as phytotherapics: e.g. *Passiflora alata, Valeriana officinalis e Avena sativa*) were used in 56.3% in parallel with the homeopathic substances. The other 9.6% did non-drug therapies. The quest for professional, loving, and financial success has been closely related to chronic stress. We have noticed that young people under 18 years of age have a strong relationship with non-adaptive diseases due to hyperactivation of the HPA axis and suffer more from acute stress. In the study cited, a total of 7 people under the age of 18 justify the 14.2% use of beta-blockers (not selective), indicated for tachycardia, migraine and vasovagal syncope. In relation to the period before andropause or menopause, the process of chronification of the organic changes and habits interferes in the development of the vasculopathies that later are aggravated in neuropathies and cardiopathies.

In Figure 1, we observed paresthesia complaints that were above 50% prior to treatment (represented by the darker line) and then became less than 50% after treatment (represented by the lighter line below). In relation to fatigue, we understand a decrease greater than 10% after treatment. Although in a lower percentage, complaints of sweating and sleep disorders were also favorable for treatment. The complaints in Figure 2 were somewhat more difficult to interpret because there was improvement in appetite in some patients. However, the rate of weight loss was very similar to the rate of weight gain. In the same way that there was improvement of the diarrhea for some patients and improvement of the constipation for others. In general, we consider improvements in nausea and vomiting to be common. Briefly, there was regulation of the peculiar intestinal habits for each complaint. We note that vitamin C has antioxidant, vasodilatory and beneficial properties to the immune system. Dyslipidemias, *diabetes mellitus* and systemic arterial hypertension cause circulatory problems. In the medical clinic it is common to use acetylsalicylic acid, beta blockers and calcium channel antagonists in patients who present a cardiovascular risk or with symptoms that can be observed in the values in figure 3 (e.g. high blood pressure and sinus arrhythmias). The cases of neuropathies and chronic heart diseases increase in prevalence to the proportion that the population grows older. The more quality of life is achieved, the more evolution and adaptation is passed from our generations to the future. And whoever reads our work in the future may have hope for new knowledge.
Figure 2

Digestive system:
- Nausea and vomiting
- Constipation
- Loss of appetite
- Diarrhea
- Weight loss
- Weight gain

Subtitle:
- After treatment
- Before treatment

Figure 3

Cardiovascular system

Subtitle:
- After treatment
- Before treatment

Heart rate
Blood pressure
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