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Research article

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

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Abstract

The article revises the neurosteroids origin as nervous tissue production 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 analysis type 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 activated brain area rhythm is synchronized with the stimuli that excited it. Our whole neuroendocrine system works in sequenced cycles. Any disorder compromises the mnemic function. There is an inhibitory corticosterone influence on the PSA-NCAM expression (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 glucocorticoids action and makes it possible to ameliorate the immunosuppressive effects related to chronic stress. Serum DHEA levels divided by serum cortisol levels can be used to correlate with the quality in aging degree.

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

Introduction

Logical connections arise to solve problems that were judged as indecipherable. Synaptic plasticity amplifies brain circuits. When strengthening such neural networks, injury to a dominant brain lobe can be compensated for by training that enables the non-dominant region use (which begins to exert greater dominance). Ma (1995) questions whether patient adaptation mechanisms involve only neuroplasticity, because structural nervous tissue regeneration has not yet become responsible for the central nervous system rehabilitation. Recovery is associated with the cognitive and memory functions that require the brain areas development 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 prevents the memorization capacity due to the rhythm destabilization in relation to 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 (Piefke, 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 the medial temporal lobe areas.

The memory imprinted on the brain tissue is represented by the neuromuscular pathway that repeats automatically. This "impression phenomenon at the cellular level" is known as engram, fundamental to associate with the physical correspondence memories. We have proteins that activate or repress the RNA formation from the DNA template. These molecules bind to the enzyme RNA polymerase that adheres to the DNA site that is called "promoter". There are binding sites with the enzyme that makes it possible to increase or not the genes manifestation: 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 in this way characteristics are expressed in varying manifestation degrees. Our body may appear heterogeneous as a mosaic in 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 time and space intervals. The DNA flexibility structure allows for several sites where the genes

expression in certain cell types is intensified or silenced and according to transcription factors specific to the tissue in question. For example, mutations in the coding sequence silencers may result in embryo non-survival 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 affected gene expression, leading the individual to develop a new characteristic.

Methodology

We adopted an explicative research with practical and experimental reports, from hospital observations. This research type is concerned with identifying the factors that determine the spectrum of what we conceptualized as “non-adaptive diseases”. That is, this research type attempts to explore the hypothalamic-pituitary-adrenal axis (or HPA axis) in relation to the adequacy between the neuro-sensory system and the motor-metabolic system (which are Anthroposophy concepts). The union of conventional medicine with alternative medicine allows broader results on the therapeutic plurality. We also use descriptive studies, since the factors determine a phenomenon requires a certain detail degree. The research allows subsidies for practical interventions with the objective of solving patients' symptoms in response to stress (which aggravates 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 mnemic alteration, dysautonomia, dizziness due to dyslipidemia, akathisia and other complaints. To reach the article objective that is to explain the adequacy between the neuro-sensory system and the metabolic-motor system, we need to review the neurosteroids concept. Based on the studies of Tsigos (2002), we divided the non-adaptive diseases into two large groups: the first set of pathologies refers to the HPA axis hyperactivation. The second group is characterized by the HPA axis hypoactivation. 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). Serums TSH and free T4 levels are normally maintained within the ranges considered during the circadian cycle. Variations in these hormones dosages are considered normal, if they remain below 5% in relation to their mean reference values. Analogously to cortisol, peak serum thyroid hormones levels 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 melatonin concentrations are inversely proportional to this described behavior. We conceived a simplified thyroid hormones regulation model, in which euthyroid patients express concentrations on each main substances involved, within temporal variations and the sleep-wake cycle. Our body tries to adapt to the clear period duration (day) and the dark period (night). However, sound, light and environmental information confuse the perception sense. The suprachiasmatic nucleus (or SCN) perceives light and influences the genes expression related to the luminous stimuli variations. 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 T4 and T3 concentrations. 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 thyroid function evaluation. Although thyrotropin production is altered, there may be only one disease without symptoms and going unnoticed or subclinical. This disease type 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 environment new information 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 insufficiency and others), medications users (e.g. lithium, cytokines, amiodarone), hypercholesterolemia, hyponatremia, anemia, comorbidities such as sleep apnea, depression or dementia. Thyroid stimulating hormone, prolactin, aldosterone, renin, testosterone and corticosteroids are related to the circadian rhythmicity (De Almondes and De Araújo, 2003).

Van Gool and Mirmiran (1986) argue that there is the sleep/wake cycle fragmentation in the elderly, taking into account their habits throughout life. Irregular work hours, leisure and meals make restful sleep difficult. The organic changes spectrum (in an attempt to adapt) decreases the immune system (through high cortisol levels). 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 amines release (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, ie, 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 rapid eye movement 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 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 endorphins release 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 aging reversion, anticancer effects and glycemic control (Chopra, 1994). This substance that is becoming popular arises from the 17-OH-pregnenolone metabolism and is converted into sex hormones (androgens and estrogens) in peripheral tissues (such as gonads). There is the 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 relation represented by the division: "serum DHEA levels / serum cortisol levels". Such division can be used in geriatric follow-up and to correlate with the quality in aging degree (De Paiva Neto, 2019). So, the DHEA increase and the cortisol reduction manifests positively in individuals who maintain a life quality, meditation and non-concern. Blood flow tends to increase from the first minute with 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 SNS action. And the metabolic syndrome itself is associated with sympathetic hyperactivation and reduced baroreflex sensitivity (Schlaich, 2015). In the obesity pathophysiology 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 nitric oxide production or activates the antioxidants action, restoring endothelial function in patients with increased peripheral vascular resistance. High vitamin C doses would act as a priority reducing superoxide anions, while their chronic oral therapy increase nitric oxide production and activate the antioxidants action, restoring endothelial function in obese individuals (Fernandes, 2011). Baulieu and Robel (1998) stated that it is possible for the nervous tissue to produce de novo steroids, that is, autonomously in relation to the peripheral glands production (originating the so-called “neurosteroids”). Regardless of where they are produced, CNS-acting hormones are conceptualized as "neuroactive steroids" that can modify the encephalic adaptation structure to environmental stimuli.

When "pregnenolone sulfate" (PregS) is administered into the hippocampus, this neurosteroid PregS reverses aging-related memory deficits in rat studies (Vallée *et al., 1997*). Regarding the human brain, Lanthier and Patwardhan (1986) conducted postmortem research, 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 PSA-NCAM expression (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 PregS action mechanism, reducing hippocampal neurogenesis. However, AlloP favors the progesterone effects on cognitive and morphological recovery, with decreased neuronal death (He, Hoffman and Stein, 2004). The explanation comes from the fact that allopregnanolone reduces the pro-apoptotic proteins expression, influencing the glial scars formation and allowing better cognitive performance (Djebaili *et al., 2005*). There is “an inhibitory influence of corticosterone on PSA-NCAM expression” (Cremer *et al.*, 2000). Melancholic depression has been described as deregulation of negative feedback in the hypothalamic-pituitary-adrenal axis (or HPA axis), associated with hypercortisolemia (Pariante 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 could be metabolic syndrome. We can also question whether these patients have polycystic ovary syndrome and hypothyroidism. Some patients may receive dexamethasone 2 mg every 6 hours for 48 hours or take dexamethasone before midnight to measure plasma cortisol the next day. The dexamethasone suppression test has been performed in severely depressed patients with surprising results: cortisol levels remain high and have no suppressive effect in response to dexamethasone use. In Cushing's syndrome, this test causes a reduction of more than 50% in ACTH secretion. Ectopic ACTH secretion remains high in extrahypophyseal tumors. Some occult carcinoid tumors may exhibit ACTH suppression, mimicking Cushing's disease. However, blood tests from the same patients demonstrate that ACTH dosage is decreased after corticotrophin releasing-hormone injection (or CRH injection). The most striking is that previous treatment with dexamethasone makes it possible to increase the ACTH secretion after the HLC injection. Therefore, some scientists choose to request the dexamethasone suppression test along with the CRH 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 diagnosing Cushing's syndrome (Castro and Moreira, 2002).

According to Tsigos (2002), some disorders may occur with the HPA axis hyperactivity, including anorexia nervosa, obsessive-compulsive disorder, panic, chronic alcoholism, alcohol or narcotic withdrawal, diabetes mellitus and hyperthyroidism. In our conducts, we requested TSH, free T4, fasting glycemia, glycated hemoglobin, lipidogram, electrolytes, electrocardiogram, basal serum cortisol, ACTH, kidney function tests, liver function tests, vitamin D, bone densitometry, pelvic ultrasound and other exams. 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-Albrigh syndrome, neuroblastoma or Wilm's tumor. Pasquali et al. (1993) demonstrated that in women (with central obesity) there was an increased plasma cortisol response when they underwent CRH 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 insulin resistance by vasoconstriction in the skeletal muscles vascularization, the descending pathways activation 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 the HPA axis hypoactivation. In this group, the corticotropin-releasing hormone (HLC) secretion is decreased. This situation occurs in patients with posttraumatic stress disorder, seasonal depression, atypical depression, chronic fatigue syndrome, hypothyroidism and fibromyalgia. Laboratorially, urinary 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. HLC concentrations in cerebrospinal fluid may be decreased (the opposite of what occurs in HPA axis hyperactivity). The frontal cortex tends to have more corticotropin-releasing hormone receptors. Some studies have aimed to relate this hormone to decreased libido and appetite, also influencing psychomotor alterations and sleep disturbances (Juruena, 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. Infradial rhythms present superior duration to the circadian rhythm, that is, the cycle of the infradiano 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 endocrine system is closely related to the chronobiology rhythmicity. The hormone secretion provides examples for all rhythms types. Each species presents a hormone secretion at different times of the day according to its needs. For various hormonal secretions such as thyrotropin, prolactin, aldosterone, renin, testosterone and corticosteroids are visible to the existence of circadian rhythmicity. Through the potassium iodide administration, short-term iodine overload may cause an increase in thyroid hormones (by the Jod-Basedow phenomenon) or block in thyroid function (by the Wolff-Chaikoff effect), with consequent hypothyroidism (Woeber, 1991). Endocrine syndromes clearly have a close relationship with our suitability between the neuro-sensory system and the metabolic-motor system. There is rhythmicity in glandular production and smooth muscle motility to preserve homeostasis (Lanz, 1988). In addition, we cannot forget irritable bowel syndrome, where emotions may interfere with altered motility or the intestinal spasm and alterations in digestive secretion (Ribeiro *et al., 2011*).

Arnaldo Paiva Neto (2019) classified the amnesia types into two major groups: in the first set, **organic causes prevailed**, and in the second, **psychological causes** prevailed. In practice, the mind works by both actions, 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 and other insufficient 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 people´s life in which the words lose the sense and they do not seem to serve. So they don't say. The trauma origins and psychological memory are exemplified in this context.

We know that in medical practice the forgetfulness origins are commonly associated with organic, structural or psychological reasons. Among the reversible dementias, their cause may be secondary to depression, hypothyroidism, vitamin B12 deficiency (after bariatric surgery, atrophic gastritis or intestinal inflammation), infections (by neurosyphilis or HIV), aluminum poisoning, drugs (illicit or licit, such as benzodiazepines), normal pressure hydrocephalus (with symptoms of dementia, apraxia and urinary incontinence). While primary dementias result from Alzheimer's disease, vascular dementia, Lewy body dementia, dementia in Parkinson's disease, frontotemporal dementia (early atrophy and neuronal loss). Albert and Ururahy (1997) listed the physical manifestations most commonly encountered 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, urticarial lesions, hair loss, psoriasis, mycosis, impotence, 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 temperature cycle, 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 a brain area 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 glands function 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 the psychic pain in the center. Psychic pain is 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 separation anguish. Primary narcissism generates a feeling of being strong. Fantasy can be represented by the thought: "I have everything at the time I need" or "I will cry so I will be protected". 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 opinion on life. Life can be seen as good or bad. These perceptions are best exemplified by the idea of the Phoenix myth that refers to the ability to overcome. On the other hand, secondary narcissism can appear. Ideas such as "I make myself happy" may arise. The big question is to find out what makes people happy. Consciousness is the window through which the inner light is externalized, being the intelligence vehicle. 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. Examples

of these effects are akathisia, dystonia, pseudoparkinsonism or dyskinesia.

For us to understand non-adaptive diseases, we need to separate patients groups as the sex hormones decreases. Menopause occurs between the ages 45 and 55. Andropause occurs between 40 and 55 years. We have characterized that younger patients predominantly present acute stress cases. 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 (Loures, 2002). Skin changes are also influenced by the stress load experienced. There is a rare disease known as red ear syndrome. Some therapeutic results were observed with the use of beta blockers. But further studies are needed to better understand this disease. Another disease called erythromelalgia is the paroxysmal vasodilation of small arteries of feet and hands. Such a disease can also affect the face, ears and knees. Patients complain of heat, redness, and pain. In some regions it is possible to apply botulinum toxin. Some physicians advocate neuropathic treatment with gabapentin, tricyclic antidepressants, or selective serotonin reuptake inhibitors (Albuquerque, 2011).

Conclusion

The steroid dehydroepiandrosterone (DHEA) inhibits the action of glucocorticoids and makes it possible to ameliorate the immunosuppressive effects of chronic stress (Pagliarone and Sforcin, 2009). There is a relation 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 this relation, except in severe and dysfunctional cases or 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 stress, anorexia nervosa, melancholic depression, obsessive-compulsive disorder, panic disorder, malnutrition, diabetes mellitus and hyperthyroidism. In relation to the second group, we divided the hypoactivation of the HPA axis associated with atypical depression, chronic fatigue syndrome, seasonal depression and fibromyalgia. 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.

According to the synchrony mechanisms classification, we call the term "category 3" referring to the hormonal variations by glands function 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 could benefit the aging process. From the vascular point of view, the use of acetylsalicylic acid and statins stands out. Some scientists have studied revolutionary pathways of pharmacological action. These pathways can become "21st-century tripod": based on "neuroesteroids," "neurogenesis," and "anti-tumor". For example, the ixolaris protein is still under study. It would block primary tumor growth and glioblastoma angiogenesis. We summarize the conclusions that we obtained after the whole research:

1. There is “an inhibitory influence of corticosterone on PSA-NCAM expression” (Cremer *et al.*, 2000);
2. PregS enhances neurogenesis through PSA-NCAM expression;
3. AlloP produces an effect opposite to the PregS action mechanism, reducing hippocampal neurogenesis. However, AlloP favors the cognitive recovery effects, with a decrease in 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 (Mezey, 2003);
5. PSA-NCAM expression and neurogenesis occur in the hippocampal region.

According to Claudia Rother and Jutta Oexle (2010), 43 physicians assisted a total of 300 individuals. 234 of the patients were women and 66 were 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 old are related to non-adaptive diseases due to hyperactivation of the HPA axis. Such patients may suffer 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. Regarding the period close to andropause or menopause, the chronicity of diseases and lifestyle habits interfere with the development of circulatory diseases. These patients may develop vasculopathies, nephropathy, neuropathies and heart diseases.

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 weight loss rate was very similar to the weight gain rate. There was improvement in diarrhea for some patients and improvement in 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. The use of angiotensin-converting enzyme inhibitors, diuretics, beta-blockers and calcium channel blockers in patients with heart disease is common. Figure 3 shows improvement in blood pressure levels and heart rate. These vital signs are related to stress levels. The neuropathies cases and chronic heart diseases increase in prevalence to the proportion that the population grows older. The healthier people live, the more adaptable they become. Those who most adapt to the circumstances will survive. Diseases also arise from the inability to adapt.

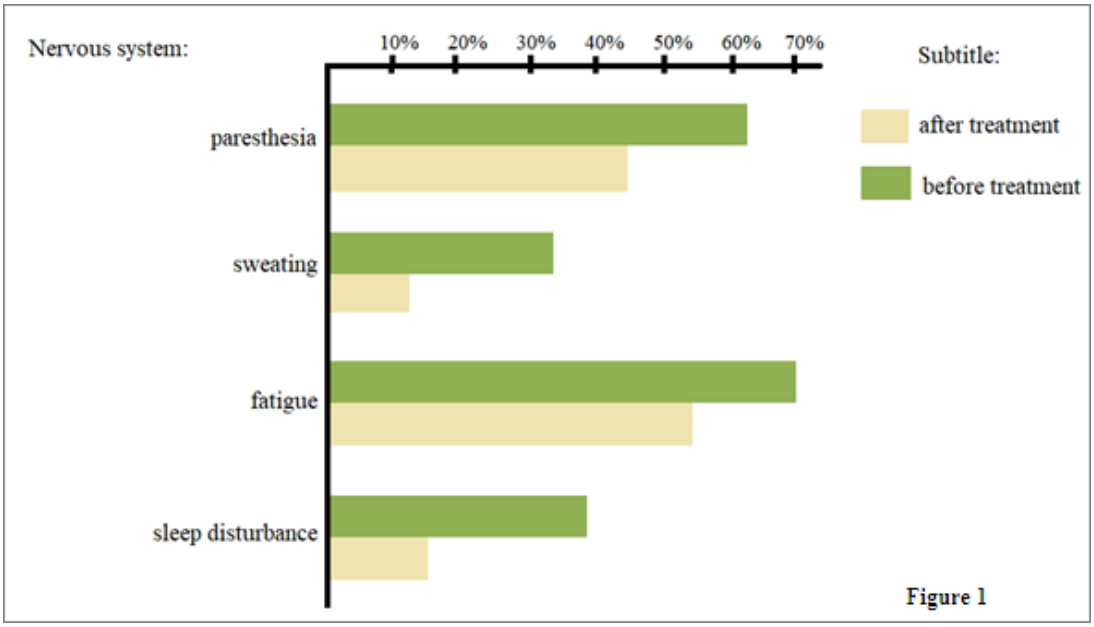


Figure 1

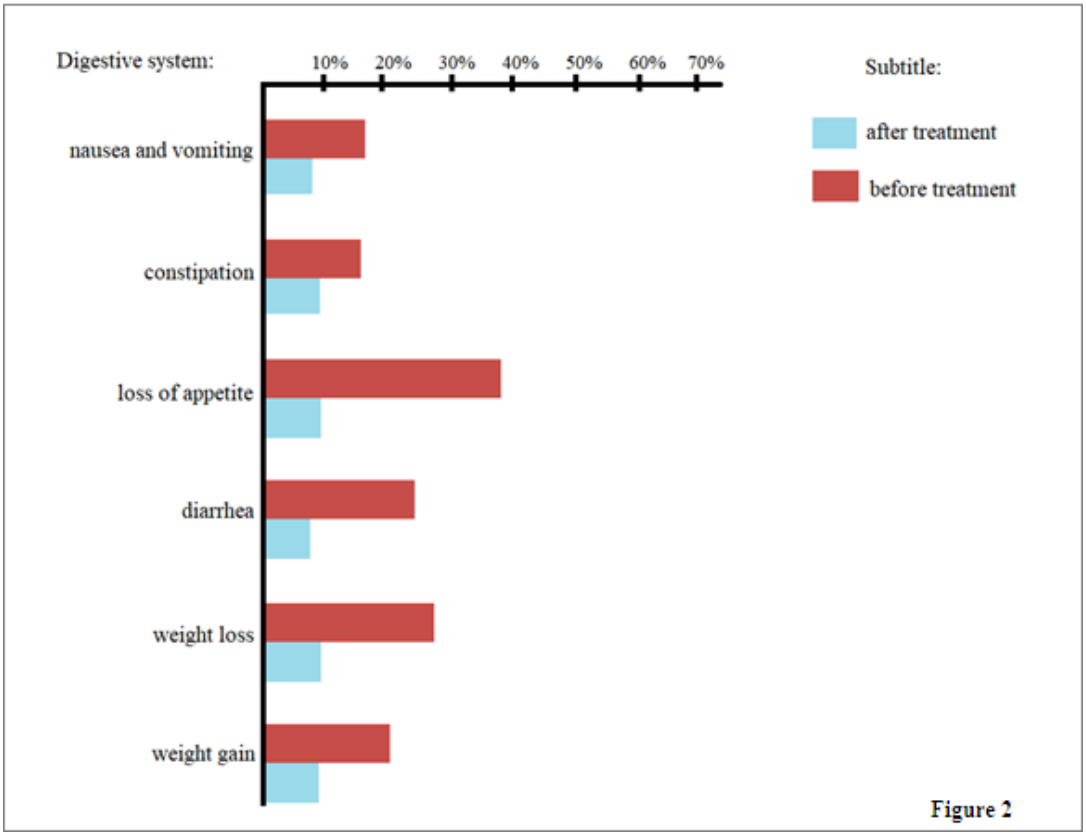
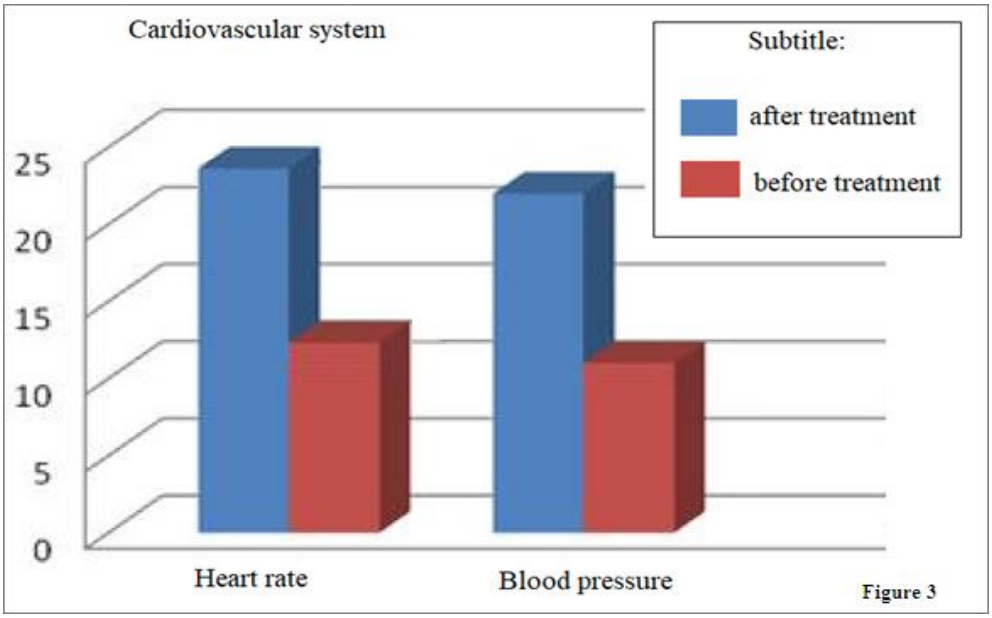


Figure 2



n = 300 patients	Therapeutic options			Total
	Beta-blocker	Other treatment or psychotherapy	Herbal medicine or homeopathic	
Polytherapy	14.2 %	9.6 %	29.5 %	53.3 %
Monotherapy	26.8 %	—	19.9 %	46.7 %
Total	41 %	9.6 %	49.4 %	100 %

Figure 4

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