Abstract

Objective: To review the literature on neurobiological findings related to hypothalamic-pituitary-adrenal axis dysfunctions associated with posttraumatic stress disorder. Method: The relevant scientific findings were described according to the date of publication and the characteristics of the studies: preclinical studies, studies on early life violence as a risk factor, and clinical findings related to patients diagnosed with posttraumatic stress disorder. Results: A rich literature on hypothalamic-pituitary-adrenal axis dysfunctions and posttraumatic stress disorder was found. Neurobiological findings showed that posttraumatic stress disorder is associated with hypothalamic-pituitary-adrenal axis dysfunctions and other brain-related structures: prefrontal cortex, hippocampus, and amygdala. Posttraumatic stress disorder patients have low plasma levels of cortisol and present increased responsivity of glucocorticoid receptors, suggesting that the inhibition of negative feedback plays a significant role in the disorder pathology. Preclinical studies using animal models of maternal deprivation showed that depending on the moment the trauma occurred during the development, different hypothalamic-pituitary-adrenal axis dysfunctions were produced. Clinical studies showed that early life stress is related to the development of psychopathologies during adulthood. Conclusions: There is robust evidence of hypothalamic-pituitary-adrenal axis dysfunctions related to posttraumatic stress disorder, and the mechanisms underlying this association are being better understood.

Descriptors: Neuroendocrinology; Stress disorders, post-traumatic; Hydrocortisone; Hydrocortisone adrenocorticotropic hormone; Corticotropin-releasing hormone

Resumo

Objetivo: Os autores realizaram uma revisão tradicional da literatura sobre os achados neurobiológicos das disfunções do eixo hipotálamo-pituitária-adrenal associados ao transtorno de estresse pós-traumático. Método: Os achados científicos relevantes foram descritos de acordo com a ordem cronológica de publicação e as características dos estudos, se eram pré-clínicos, relacionados à violência precoce como fator de risco e, finalmente, achados clínicos em pacientes portadores de transtorno de estresse pós-traumático. Resultados: Foi encontrada uma literatura rica de achados a respeito de disfunções do eixo hipotálamo-pituitária-adrenal e transtorno de estresse pós-traumático. Os achados mostraram que o transtorno de estresse pós-traumático está associado a disfunções deste eixo e de estruturas cerebrais como o córtex pré-frontal, hipocampo e amígdala. Os pacientes com transtorno de estresse pós-traumático apresentam um aumento da responsividade dos receptores de glicocorticóides, sugerindo que a inibição do feedback negativo tem um papel importante na fisiopatologia do quadro. Estudos pré-clínicos com modelos animais de deprivação materna evidenciaram que, dependendo de quando o trauma ocorre, a disfunção do eixo será diferente. Os estudos clínicos mostram que o estresse precoce está relacionadas ao desenvolvimento de psicopatologia durante a vida adulta. Conclusões: As disfunções do eixo hipotálamo-pituitária-adrenal relacionadas ao transtorno de estresse pós-traumático são evidências robustas e os mecanismos subjacentes a ele são cada vez mais compreendidos.

Descritores: Neuroendocrinologia; Transtornos de estresse pós-traumático; Hidrocortisona; Hormônio adrenocorticotrófico; Hormônio liberador de corticotropina

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Introduction

The DSM-IV criterion A for posttraumatic stress disorder (PTSD) requires the presence of a stressor event that threatened the subject's emotional or physical integrity creating horror or despair. PTSD diagnosis has three clusters of symptoms: 1) reexperience of the traumatic event, 2) avoidance and numbness, and 3) hyperarousal.

Image revivals happen in the form of intrusive memories, persistent reminiscences, and traumatic nightmares followed by psychological distress and physiological reactivity. Avoidance is the effort to avoid thoughts, feelings, activities or people related to the trauma. Numbness could present as a decreased interest in daily activities, feeling of detachment, and restricted range of affect. The hyperarousal cluster is characterized by symptoms of insomnia, irritability, difficulty in concentrating, hyperarousal, and exaggerated startle response.

Studies on the hypothalamic-pituitary-adrenal axis (HPA) and the autonomous nervous system (ANS) are critical since they establish a relationship between body/mind and the environment. Thinking in a simplistic way, we would be tempted to look for a hyperactivation of these systems, but scientific findings show a different reality.

The prefrontal cortex, the hippocampus and the amygdala are related to the HPA axis. The hippocampus and the prefrontal cortex are mostly inhibitors, while the amygdala activates the HPA. The HPA axis is highly sensitive to external changes, which are the focus of PTSD studies. The response to glucocorticoids (GC) could be initiated by direct activation of paraventricular nucleus by nociceptive pathways (pain), innate defensive responses (predators aversion) or multimodal sensorial association (e.g. conditioned fear).

These cerebral structures are deeply related to the hypothalamus, where the corticotrophin release hormone (CRH) is produced by hypophysiotropic neurons at the medial parvocellular nucleus of the paraventricular nucleus (PVN). Many studies connected the hippocampus to the HPA axis. Hippocampal stimulation decreases corticosterone in rats and cortisol in humans, suggesting that this region inhibits HPA axis activation.

The prefrontal cortex is also implicated on stress regulation. Anterior cingulate cortex and lesions of the prelimbic division increase adrenocorticotropic hormone (ACTH) and corticosterone secretion in rats and induce CRH production by PVN after forced restraint, suggesting a specific stressor role in the HPA axis inhibition.

It is supposed that the amygdala activates the HPA axis. Its influence is highly mediated by central and medial amygdaloïd nucleus, representing the most important amygdala projection to brain stem, hypothalamus, and midbrain. Amygdaloïd lesions reduce corticosterone or ACTH after stress, while stimulation increases the HPA axis activation.

Preclinical studies

Maternal deprivation models with rodents and variable foraging demand in primates have shown that depending on which development stage the stress occurred, different results would be determined; it was called ‘timing effects’, leading to a hypo- or hyperactivation of the HPA axis during the animal adulthood. These findings have shown that early life events are powerful risk factors, and apparently if these events happen during specific development periods such as adolescence the subjects have a higher risk for PTSD.

At the same time, other studies with enriched environment have produced opposite findings regarding behavioral and hormonal responses to stress. Branchi et al. have studied rats raised at communitarian nests, a richer early social environment similar to the wild form of nests of many rodent species. They have found that rats raised at these nests have more ability to interact socially, and their acquisition of social behavior patterns was faster, either for dominant or subordinate behavior, than those rats raised isolated. The former has higher levels of neuronal growth factors such as brain-derived neurotrophic factor (BDNF) levels. The authors have concluded that a socially rich environment is associated with better social life during adulthood, and those are associated by a markedly change in neurotrophins at selective brain areas like the hippocampus and the hypothalamus.

Prolonged stress ends with an increased glucocorticoid and catecholamine secretion by the adrenal. Prolonged glucocorticoid exposure causes the destruction of the neurons located at the CA3 region of the hippocampus, reducing glucose and increasing calcium entries in these cells. Due to increased glutamate and glucocorticoid levels, a greater calcium mobilization is generated by N-methyl-D-aspartate (NMDA) and alpha-aminohydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors activation and an activation of an intracellular system of second messengers leading to a cellular cascade effects. Cellular mechanisms try to recapture glutamate from synaptic cleft or tamponate calcium ions to avoid free radicals accumulation and cell death.

Gould et al. have demonstrated the deleterious effects of glucocorticoid on neurogenesis. Neurogenesis reduction, neurotoxicity, and impairment of the neuron ability to survive seem to be responsible for the hippocampal atrophy described in some patients with PTSD.

New studies should figure out how this hippocampal atrophy occur. Some studies have suggested that many neurotransmitters like serotonin, dopamine, and noradrenaline play a role in this process. Also, low cortisol levels and high CRH levels can contribute to the atrophy. The intricate mechanisms of the organism reaction to violence could be better known with the advance of preclinical studies.

Violence against children and teenagers

Among the risk factors for the development of PTSD during adulthood, exposition to traumatic events, particularly during childhood, has a significant role. Such predisposition could vary according to frequency, intensity, and duration of past traumatic events. However, it is unspecific, since it occurs in other disorders like mood disorder, anxiety, substance abuse, and conduct and personality disorders.

Breier et al. have recruited subjects with history of parental separation and have found a high proportion of subjects with psychiatric conditions. These subjects had higher cortisol basal levels compared to controls. Heim et al. have conducted many neuroendocrinological investigations looking for correlations between early trauma, depression, and HPA axis function. They have found that a trauma report, more than a major depressive disorder diagnosis, led to HPA axis dysfunction. Multiple regression analysis of these data has revealed that traumatic history was related to stress hyperactivity, and that the interaction between child abuse and trauma was the greater predictor of responsivity to ACTH.

Carpenter et al. have studied the CRH on spinal fluid (CRH/SF) concentration of 27 depressed, medication free individuals
and 25 paired controls. The perceived stress levels during the pre-school and pre-adolescence years have been verified with a self-report scale. The difference between the means of CRH/SF of patients and controls has not shown statistical significance. However, a regression model has shown that the stress perception was a powerful predictor of CRH/SF alteration, while depression has not had this power. Perinatal adversity and pre-adolescence years have been independently associated with CRH concentration.

Maercker et al. have interviewed young adults from Dresden regarding the occurrence of traumatic events, depressive, and PTSD uprising symptoms. The sample was subdivided into subjects with traumas during childhood (up to 12 years) and subjects with traumas during adolescence (after 13 years). They have found that a quarter of the sample reported a traumatic event. Those who reported a traumatic event during childhood had odds ratio (OR) of 5.18 to develop depression compared to 0.91 to develop PTSD. Those who reported a traumatic event during adolescence had an OR of 0.19 to develop depression compared to 1.10 to develop PTSD.

The initial clinical findings have confirmed that the presence of early adversity, particularly during susceptible periods, is an important risk factor for PTSD development during adulthood.

**Clinical studies**

The clinical studies with PTSD patients are providing the first scientific evidence on HPA axis dysfunction. The first studies have evaluated catecholamines and their relation with basal cortisol. Lemiux et al. have evaluated norepinephrine, dopamine, and cortisol on 24-hour urine from 28 women (11 with PTSD and abuse during childhood, 8 with abuse during childhood without present PTSD, and 8 women without abuse or PTSD). The patients with PTSD had significantly higher norepinephrine, dopamine, and cortisol levels, differently from other findings with male veterans with PTSD. The authors have credited this difference to the age of exposure to the traumatic experience.

Mason and Jacobs have found a higher norepinephrine/cortisol ratio in PTSD patients; they have speculated that it happened due to a norepinephrine increment and not a cortisol elevation. Studies with veterans have shown different findings compared to studies with women. Boscarino et al. have found that veterans with PTSD had lower cortisol levels, and these findings are related to the presence of PTSD diagnosis. Veterans with a past diagnosis of PTSD did not show this HPA dysfunction, suggesting that the traumatic effect tends to disappear with time and clinical improvement.

Yehuda et al., in a series of studies, have confirmed the findings of Boscario et al. They have found that the dysfunction was related to specific traumas. The dysfunction was found when the traumatic event occurred during combat operations, and not in veterans who presented PTSD after they were back at home. The same finding has been observed in Holocaust survivors with PTSD compared to those without PTSD and normal controls, only the formers had lower cortisol levels. Therefore, the authors have affirmed that there are differences in the neurobiology of specific traumas depending on the moment they affected the subject. The low cortisol level is probably related to significant traumas that lead to the development of PTSD, and it remains symptomatic.

Again, the productive group from New York, trying to further investigate PTSD of the HPA axis dysfunction, has evaluated cortisol and GC receptors after the dexamethasone suppression test (DST) in 23 Holocaust survivors, 27 veterans, and 10 healthy controls. They have found a higher cortisol and GC lymphocyte receptor suppression in older trauma survivors with PTSD compared to survivors without PTSD and controls. The dexamethasone responses were not related to PTSD severity, but to the number of years after the traumatic event and the presence of PTSD symptoms.

Studying civilians, Young and Breslau have evaluated a representative sample from the community (n = 1,200). This sample differed from patients who looked for specialized services, an indicator of the severity of trauma and the symptoms specificity. In this sample, 265 subjects had been exposed to trauma and 68 had a present or past PTSD diagnosis. The exposed group with PTSD had a higher salivary cortisol level in the evening compared to the non-exposed group. When comorbidity with major depressive disorder (MDD) was analyzed, only the subjects with this comorbidity had the increased cortisol level. People with PTSD alone did not differ from controls regarding salivary cortisol levels. These data suggest that, in these cases, the PTSD was probably milder because the traumas were not so violent (difference between violence and barbarity) compared to those of Holocaust survivors or veterans, and did not present the same HPA axis dysfunction, which suggests that the PTSD diagnosis must be reformulated to become less inclusive.

Using the same sample, they have analyzed urinary catecholamines collected during two consecutive nights. The group with PTSD diagnosis had significantly higher levels of catecholamines compared to the exposed group without PTSD diagnosis and the non-exposed group. Those exposed to violence, but without PTSD diagnosis, had significantly lower catecholamines levels compared to the individuals from the other groups. The cortisol levels did not differ between the groups; when analyzed regarding the comorbidity with depression, the group with PTSD only did not differed from the group without PTSD or MDD. Women with MDD and PTSD had significant higher levels of cortisol. The authors have concluded that trauma in itself did not lead to a sustained cortisol or catecholamines elevation. PTSD is associated with higher catecholamines levels, however, PTSD subjects did not have urinary cortisol levels alterations. It is possible that these data might be replicated with a specific sample of civilians with PTSD diagnosis.

Rhoeleder has studied the GC receptor sensibility through interleukin 6 (IL6) and alpha tumor necrosis factor (TNF-α) concentrations after dexamethasone (DEX) ingestion in 12 refugees from Bosnia with PTSD and 13 controls. The PTSD patients were non-responders in the morning and the levels did not increase during the day. They needed a lower DEX dose to suppress cytokines; the IL6 production was significantly increased in patients, but not the TNF-α production. The authors have concluded that refugees with PTSD had hypocortisolism associated with higher sensitivity of the immunological tissues to GC. The findings by Yehuda et al. of an increased sensitivity to GC receptors in PTSD patients started to be replicated by other groups. Bremner et al. have studied 52 women with PTSD with and without sexual abuse during childhood through a HPA axis evaluation. Women with abuse history and PTSD diagnosis had lower cortisol levels in the evening compared to women without PTSD. The ACTH response to the CRF challenge test was blunted compared to not abused women (but not for those without abuse and PTSD). There were...
not differences between ACTH responses to CRF. High levels of symptoms were associated with low levels of cortisol in the evening. These findings lead to the conclusion that early abuse is associated with CRF elevation, suggested by a decrease in hypophysis sensitivity to CRF, as well as abuse with PTSD was associated with more pronounced hypocortisolemia at noon.

Lindauer et al. have studied 24 Dutch policemen, 12 with PTSD and 12 exposed to violence but who did not develop PTSD. Among those with PTSD, 8 had been exposed to interpersonal violence and four to accidents. Three of them had overlapped depressive symptoms, with mild to major depressive disorder after the PTSD onset, which was the main diagnosis. Subjects with PTSD had a smaller hippocampal volume on both sides. Subjects with PTSD had higher salivary cortisol compared to controls. PTSD subjects presented more perseverations and were prone to have more intrusions and worse working memory. These findings showed an opposite result: a specific group of subjects, police officers with PTSD, had an increase in cortisol, which the authors linked to damage to hippocampus and memory.

Gunnar et al. have studied serial salivary cortisol concentrations of 18 Rumanian orphans who stayed at an institution for at least 8 months under very poor care conditions compared to 15 orphans who were adopted earlier and stayed for less than 4 months at the institution and 27 children raised by their own families from British Columbia (Canada). Sali va samples were collected when the children had been adopted for at least 6 years. Rumanian orphans had a lower cortisol mean than the other both groups. There were no differences between the groups with an earlier adoption and that of children born in Canada. The longer the orphans remained institutionalized, the more pronounced was the HPA axis dysfunction, the lower their IQ and their height. The two last factors, however, did not interfere with cortisol. This finding showed that small children exposed to persistent and severe violence have reduced cortisol levels.

Trying to further investigate hypocortisolemia, Yehuda et al. have studied veterans with and without PTSD using the Dexamethasone Suppression Test (DST) to evaluate the negative feedback of GC concentrations and their relations with cortisol in response to a low dexamethasone dose (0.5 mg). They have studied 29 men, and 9 women (19 with PTSD and without PTSD). They have found a significant ACTH and cortisol reduction after DEX in subjects with PTSD compared to those without PTSD.

These findings suggest that low cortisol levels after DEX are not due to low cortisol production by the adrenal or low adren al sensitivity to ACTH. This study enhances the hypothesis of a negative feedback increase induced by cortisol leading to an ACTH production inhibition. PTSD is associated to ACTH secretion inhibition by the hypophysis produced by increase in the negative feedback induced by cortisol.

Although a great ACTH decrease after DEX has been found in PTSD patients, this finding did not explain much about central responsivity, since dexamethasone does not easily penetrate the hematoencephalic barrier.

Trying to evaluate the central responsivity, Yehuda et al. have evaluated veterans with and without PTSD, who received daily low doses (17.5 mg/day) of intravenous (iv) hydrocortisone or placebo during two weeks. The PTSD patients had a greater ACTH decrease reflecting a higher GR responsivity to cortisol. In spite of the fact that cortisol has a better ability to trespass the hematoencephalic barrier than dexamethasone does, it is excreted from brain through steroids transporters such as P glycoproteins. Even with a 2.5 increase in plasma cortisol concentration after the hydrocortisone injection, we cannot assert that it was enough to saturate the brain excretion pumps, producing a central action. However, the low levels of ACTH demonstrated increase responsivity to GC in PTSD, which might reflect central alterations of GC.

Inslicht et al. have studied basal salivary cortisol levels in 49 women who were exposed to domestic violence (15 with present PTSD, 14 with past PTSD, and 20 without PTSD). A correlation between the time of trauma exposure and high concentrations of salivary cortisol was found. The more recent the trauma, the higher the cortisol level. The PTSD group (past and present) had higher cortisol levels, even when the data was controlled by drugs that affect the axis. The abused group had more scores of depression on the HCL-90, but the presence of depression did not correlate with neuroendocrine findings. The same was true for the comparison between women with a present depressive episode and those without a depressive episode (using the SCID-I).

The study showed that women with lifetime PTSD have increased cortisol levels. The sample results were obtained from the community sample; people who did not spontaneously looked for a mental health service. Similarly to the study by Breslau et al., the data suggest that it is possible to find different pathophysiology depending on specific trauma and population.

Santa Ana et al. have examined the HPA axis and subjective stress regarding a physical stressor (hand immersion in cold water) in 89 patients with PTSD. ACTH, cortisol, and subjective stress were measured before and after the test. Individuals were divided into controls (31), with PTSD due to trauma during childhood (25), and PTSD due to trauma during...
adulthood (33). A consistent finding was that 48% from the traumatized group were alcohol dependent.

Subjects with PTSD, regardless of the moment they suffered the trauma, showed a less robust response to ACTH. Also, in spite of the presence or absence of alcohol dependence, victims of trauma during childhood had lower basal cortisol and lower cortisol concentrations at all measures after the physical stress. Patients with trauma during adulthood did not show a recovery of cortisol levels up to 2 hours after the end of the test.

Otte et al., looking for alterations on mineralocorticoids receptors (MR), have studied 11 patients with PTSD compared to 11 controls. The subjects were treated with 4 g of metyrapone (to inhibit cortisol production from the adrenal). On the next day, they received 0.5 mg of fludrocortisone, a MR agonist or placebo. ACTH, cortisol, and 11-deoxycortisol were evaluated every 30 minutes from 2 am to 9 pm on blood samples. Comparing placebo to fludrocortisone, the latter decreased significantly ACTH and cortisol levels on both groups. Patients with PTSD had higher cortisol and ACTH levels after metyrapone, reinforcing the increased sensitivity of GR in PTSD patients, but there were not differences with the use of MR agonist, leading the authors to postulate that there are no differences regarding MR in the HPA function of PTSD patients and normal controls.

Griffin et al. have applied the DST (with low dose 0.5 mg) on 70 women victims of violence and 14 controls without trauma history or psychiatric diagnosis. Among the victims, 15 had PTSD, 27 PTSD associated with depression, and 8 did not have PTSD or depression. The victims of violence with PTSD, with or without depression, had lower cortisol levels compared to the other groups. The victims of violence with PTSD without depression had a higher dexamethasone suppression compared to the healthy individuals and the group with PTSD and depression. Again, the evidence of increased GC receptors sensitivity hypothesis and the finding of low levels of cortisol in victims with PTSD were reinforced.

Discussion

The scientific evidence of HPA axis responses of PTSD patients suggests that susceptible individuals exposed to extreme violence have a persistent reaction to the stressor. A great GR responsivity leads to a decrease in ACTH and cortisol production. The low cortisol level could be unable to “turn off” the LC-SNS system causing autonomic hyperactivation (leading to an increment of catecholamines levels). The increased CRF could be partially responsible for symptoms like insomnia, irritability, difficult concentrating, hyperarousal, and exaggerated startle response found in PTSD patients.

Imaging studies of PTSD patients showed consistent data of a decreased hippocampus volume. This finding could be partially related to a hyperactivity of the HPA system.

Functional imaging studies show hyperactivation of the amygdaloid nucleus and a blunted answer from the prefrontal medial cortex and anterior cingulum gyrus. These findings are consistent with memory reverberation (limbic and temporal hyperactivation) and the lack of experience elaboration, carried out by prefrontal cortex, with neural network distributed throughout the cortex, and creation of representation.

The memory reverberation remains, since it is often present (persistent reminiscences) with concurrent somatic symptoms (hyperarousal). The subject lives as if the trauma was going to happen again at any minute, and he/she needs to make any efforts to avoid it (avoidance).

There is not any elaboration of the traumatic experience. It is not incorporated to the self. The individual with PTSD feels unable to act in order to avoid the imaginary trauma, which could happen at any time. He/she does not trust his/her ability to act or decide.

The memory reverberation creates confusion between imagination and reality. The individual loses the perception of reality. The understanding of reality and the present time is distorted by the perception and the action.

To understand the reality, the individual needs a healthy mental functioning. A dysfunction of this mechanism could lead to memory reverberation, ideas of disability, insufficiency, and anxiety. This psychopathology has a pathophysiological correspondence.

We can formulate that the mental process for a susceptible subject to become ill is caused by an intense traumatic experience. This subject creates a persistent sensation of an imaginary danger, and feels that it is real. The organism reacts with a HPA axis hyperactivation. It is possible to raise the hypothesis that due to the intensity of the experience (in a susceptible subject due to an early life stress) the sensitivity of the GC receptors increases, decreasing the ACTH and cortisol production. The imminence of danger feelings leads to sympathetic activation persistence, since the low plasma cortisol level is unable to “turn it off”.

These hypotheses try to correlate scientific and clinical data. New studies must be proposed to increase our knowledge on the psychological consequences of violence in human beings. Medicine and psychology must look for new diagnostic methods and more effective treatments of violence victims. The search for innovation will be more effective if based on scientific evidence.

References