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New Concept: Endocrine Dysfunction in Post-Traumatic Stress Disorder (PTSD): The Role of Ionotropin

Fred Chasalow[1,2]* and Sandra Blethen[3]

[1]*IOMA LLC, California, USA*

[2]*Visiting Professor, Department of Laboratory Medicine, VAMC, San Francisco, CA*

[3]*Chief Medical Officer, IOMA LLC, California, USA*

***Corresponding Author:** Fred Chasalow, IOMA LLC, California, USA.

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Abstract

Post-traumatic stress disorder (PTSD) is a mental health condition that's triggered by a terrifying event. Symptoms may include flashbacks, nightmares and severe anxiety, as well as uncontrollable thoughts about the event. The diagnosis is based solely on psychiatric symptoms. Many patients also have endocrine features, including lack of REM sleep, hypertension, and a poor response to dexamethasone-suppressed ACTH challenge. These symptoms have been considered as sporadic independent features. In this concept paper, we propose that these features are not independent, but are all part of a self-reinforcing endocrine cycle. Ionotropin has a critical role in the cycle. An understanding of the cycle suggests several new potential therapies for PTSD and, potentially, a new insight into essential hypertension.

Keywords: *PTSD; GH Deficiency; Corticosterone; ACTH; Ionotropin; Hypertension*

Abbreviations

PTSD: Post-Traumatic Stress Disorder; CRF: Corticotropin Releasing Factor; GH: Growth Hormone; ACTH: Adrenocorticotropic hormone; Dex: Dexamethasone; REM: Rapid Eye Movement While Sleeping; ENaC: Epithelial Sodium Channels; TBI: Traumatic Brain Injury

Introduction

Many soldiers experience situations of extreme stress and trauma. Similar stress can also occur in civilian life. Nearly everyone will experience a range of responses to stress and trauma, but for some people, the symptoms persist for many months. The DSM-5 phenotype for diagnosis of PTSD includes: [a] re-experience, [b] avoidance, [c] arousal and reactivity and [d] cognition and mood. To make the diagnosis, candidates must have all four psychiatric features every month.

Using the DSM-5 phenotype to identify patients with PTSD, investigators have identified several characteristic endocrine findings. Typically, individuals have: [a] altered patterns of rapid eye movement (REM) sleep, [b] low cortisol response to ACTH when measured after dexamethasone suppression (dex-ACTH), and [c] are often hypertensive. However, there is no unifying concept that explains the endocrine features. It is our hypothesis that the endocrine findings reported to date are all manifestations of a single endocrine process rather than multiple independent processes. The theory was originally described at the 2019 Endocrine Society meeting in New Orleans [1].

Schematic description

The cycle is summarized in figure 1. Green arrows indicate events that are stimulated in patients with PTSD and red arrows indicate events that are decreased in patients with PTSD. The black arrow indicates a process with unconfirmed changes in these patients. Following is a description of the processes that are involved in the cycle and the changes that occur in patients with PTSD. Each section has two parts. Part 'a' briefly describes the normal action and Part 'b' describes the changes that occur in patients with PTSD.

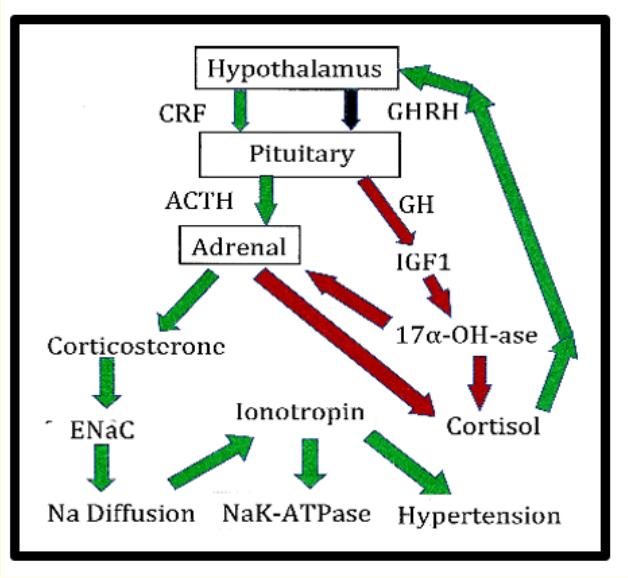

Figure 1: *Schematic Description of the Cycle. Green arrows connect processes that are increased in patients with PTSD. Red arrows connect processes that are decreased in patients with PTSD. The black arrow marks a process whose relationship to PTSD is not yet known. The block in GH secretion could be at either part of the hypothalamic-pituitary axis.*

Hypothalamus-Pituitary axis

The hypothalamus regulates endocrine function by producing specific releasing factors that are transported by a portal shunt to the pituitary. The pituitary then releases a specific hormone into the general circulation where it regulates the function of a peripheral endocrine gland. The two factors that change in patients with PTSD are corticotropin releasing factor (CRF) and growth hormone releasing hormone (GHRH). These function by stimulating the anterior pituitary to secrete ACTH and GH, respectively. When ACTH stimulates the secretion of glucocorticoids, some returns to the hypothalamus and pituitary to regulate the continuing release of CRF. The regulation of growth hormone (GH) is more complex. There are both releasing factors, GHRH, and inhibitory factors, somatostatin. Insulin-like growth factor (IGF1) is produced by peripheral tissues in response to GH. It has both local and systemic actions. Most circulating IGF-1 is produced in the liver.

PTSD patients frequently lack REM sleep and, consequently, might be expected to be GH deficient [2]. Pre-pubertal children with PTSD would be expected to experience slow growth, just like children with psychosocial growth failure [3]. In addition to IGF-1 deficiency, adults with GH deficiency experience reduced sweating and reduced ability to thermoregulate [4]. This is the only GH function not mediated by IGF-1.

Growth Hormone (GH) and IGF-1

Because GH secretion is pulsatile and circulating GH has a short half-life, a single GH measurement is unlikely to be adequate for determining GH status. However, IGF-1 has a much longer half-life and IGF-1 measurements are often used as a screening test for GH status.

There are no published studies of IGF-1 levels in patients with documented PTSD. Undurti measured IGF-1 levels in young combat veterans who had a history of traumatic brain injury (TBI) and compared them to a control group of deployed veterans who had no history of TBI [5]. There was no difference in the IGF-1 levels between the two groups. However, only 3 of the subjects had an IGF-1 level over 160 ng/ml. There are many factors that affect IGF-1 levels. In a study of normal men, Chanson measured IGF-1 levels with 6 different assays. He found that the IGF-1 levels on men aged 20 - 30 years old had a mean of 250 ng/ml and the 3rd centile level was about 160 ng/ml [6]. This suggests that most young with a history of combat have a significant degree of IGF-1 deficiency. In fact, this suggests that over 90% of deployed veterans were probably IGF-1 deficient, whether or not they had a history of TBI or PTSD.

Adrenal - Glucocorticoid Synthesis

In response to ACTH, the adrenal cortex produces both cortisol and corticosterone. The difference in structure between the two compounds is that cortisol has a 17α-hydroxy group and corticosterone does not. Corticosterone can't be converted to cortisol or vice versa. Corticosterone is a potent mineralocorticoid, cortisol much less so. Conversely, cortisol is a potent glucocorticoid, corticosterone much less so. In humans, about 95% of the glucocorticoid potency is contributed by cortisol. While ACTH is the primary regulator of cortisol secretion, GH regulates the level of 17α-hydroxylase and thus controls the relative amounts of cortisol and corticosterone actually produced. Figure 2 shows glucocorticoid response to insulin-induced hypoglycemia in children [7]. The study included 13 children with GH deficiency and 30 children with normal growth rates. The child in Panel A was GH deficient and had low IGF1 levels. The child in Panel B was not GH deficient [7]. The ratio of corticosterone to cortisol was about 0.12 in Panel A and 0.03 in Panel B. Thus, the ratio of corticosterone to cortisol was 4 times higher in children with GH deficiency when compared to children with normal GH levels. Moreover, in the GH deficient samples, the increased corticosterone secretion did not compensate for the decrease in cortisol secretion. In 1985, we showed that GH deficient children over secreted corticosterone in response to Dex-suppressed ACTH tests [8]. Three days of GH therapy normalized the corticosterone response [7]. In summary, patients with GH deficiency have reduced 17α-hydroxylase activity and that activity is restored with replacement hormone therapy.

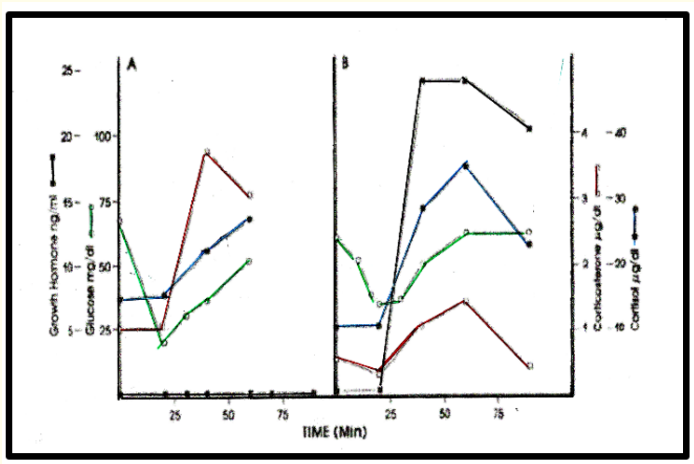

Figure 2: *Response to insulin. Induced hypoglycemia in a child with GH deficiency (Panel A) and a short child without GH deficiency (Panel B). At time zero, each subject received 0.1 unit/kg of regular insulin as an intravenous bolus. Note the exaggerated decrease in serum glucose levels in the GH deficient child and the increased ratio of corticosterone to cortisol when compared to the child without GH deficiency. Green line - glucose; Red line- cortisol; Blue line corticosterone; Black line - GH.*

Yehuda used the Dex-suppressed ACTH test to investigate serum cortisol levels in patients with PTSD [9]. The cortisol response was about half that observed in control subjects. However, Yehuda did not evaluate corticosterone response to ACTH. In summary, as many patients with PTSD are GH deficient, they would be expected to secrete 3 - 4 times as much corticosterone as individuals without GH deficiency. The extra corticosterone secreted would bind to the mineralocorticoid receptor, internalize the receptor and increase synthesis of epithelial sodium channels (ENaC).

ENaC - Epithelial Sodium Channels:

Epithelial Na^+ channels (ENaC) provide for energy-independent Na+ diffusion. In the kidney, this is the process that recovers Na^+ ions from the nascent urine into nascent plasma and in other tissues, allows passage of Na^+ ions from extracellular fluids into intracellular fluids. No energy is required by ENaC as the direction of transport is always from high Na^+ fluids to low Na^+ fluids. ENaC is synthesized in response to activation of the mineralocorticoid receptor. The main ligands at the receptor are aldosterone and corticosterone. There is sufficient salt in the American diet that salt wasting is rare. In response to ACTH, corticosterone is synthesized in the adrenal cortex. Sufficient corticosterone is synthesized in response to ACTH to avoid the need for aldosterone.

Many patients with PTSD are GH deficient and have low levels of IGF-1. They would secrete about 8 times as much corticosterone as is secreted by individuals without GH deficiency [7]. ENaC would be over-expressed and Na^+ would diffuse through its channels into the intracellular compartments. To maintain osmolality, K^+ diffuses from the high K^+ intracellular compartments to the low K^+ fluids, such as blood. This process is also energy independent.

Ionotropin - Endogenous potassium sparing hormone:

St. Gyorgyi proposed that to account for the function of digoxin, there was an unknown endogenous hormone [10]. Hamlyn, starting with 80 liters of plasma, isolated 11 µg of a digoxin-like material (DLM) that he thought was ouabain and, based on its endogenous origin, he called it "endogenous ouabain" [11]. There are more two hundred papers (of which we are the authors of 7) describing elevated serum levels of DLM and/or endogenous ouabain in various diseases [12]. However, Baecher established high sensitivity LC-MS-MS method and failed to detect any ouabain-like material in human serum from samples known to contain ouabain-like material in serum samples by immunoassay [13]. Thus, the chemical identity of the material detected as 'endogenous ouabain' is unclear and Nicholls suspects it is a fantasy [14].

Ionotropin is our candidate for the digoxin-like material (DLM) [15]. Its structure is unusual in two ways: [a] it is a phosphocholine ester and no other steroid phosphocholine esters have been identified and [b] it has the same basic 4-ring structure of other steroids but has 23 carbon atoms; there are no other steroids known with 23 carbon atoms [15]. Figure 3 compares the structure of Ionotropin to spironolactone. Both compounds are **γ-**spiral lactones. Spironolactone is a synthetic compound that acts as a K^+ sparing diuretic [a] by causing the NaK-ATPase to pump K^+ into cells and Na^+ to be eliminated and [b] by improving heart function, perhaps like digoxin. We have proposed, on the basis of its structural similarity, that Ionotropin has similar functions to spironolactone and to cardiotonic glycosides. There is a general misunderstanding that the NaK-ATPase requires ATP to transfer Na^+ into cells. No ATP would be needed for that process. ATP is needed to transfer K^+ from serum into the cells against the natural gradient. An unknown DLM, perhaps endogenous ouabain, is present in serum from patients with some forms of hypertension [16], but the only DLM we found in serum was Ionotropin [15].

In support of our theory, we found Ionotropin in fluids with high K^+ levels. There are two types of human breast cyst fluids: Type 1 have high K^+ levels (60 - 100 mM) and Type 2 fluids have modest K^+ levels (5 - 10 mM). Type 1 fluids have high levels of DLM (0.6 ng/

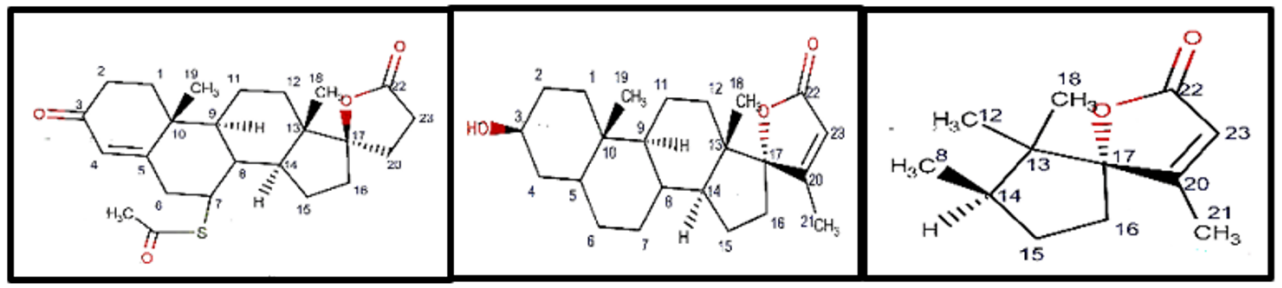

Figure 2: *Structures. Left: spironolactone; Center: Ionotropin; Right: the spiral surrounding carbon-17.*

ml) while Type 2 fluids have low levels of DLM (< 0.05 ng/ml) [17]. The DLM was extracted, LC-chromatographed and each fraction was immunoassayed for DLM. There was only one peak detected by immunoassay for digoxin. This material was purified to homogeneity and assigned the name Ionotropin [15]. In summary, the high K^+ fluids had high levels of Ionotropin.

The proposed structure of Ionotropin and spironolactone are both steroid spiral lactones (Figure 3) and could be expected to have similar functions as potassium sparing regulators. This would be necessary to compensate for the increased Na^+ diffusion caused by excess synthesis of ENaC in patients with PTSD.

Hypertension

Dietary salt has been recognized as a major risk element for essential hypertension. A model for essential hypertension is the angiotensin-treated mouse on a high salt diet. However, a 'knock out' mouse with a defective ouabain binding site doesn't get hypertension [18]. Hamlyn interpreted this to suggest a role for 'endogenous' ouabain in salt-sensitivity [16]. Further, Hamlyn proposes that endogenous ouabain inhibits NaK-ATPase. We propose that Ionotropin stimulates the ATP-dependent transport of K^+ ions into cells. A role for the NaK-ATPase to transport Na^+ ions into cells isn't needed as ENaC does the job without needing ATP.

One of the typical findings in patients with PTSD is hypertension [19]. Our concept is that PTSD patients with hypertension: [a] have high levels of DLM, [b] that the DLM present is Ionotropin (not endogenous ouabain), and [c] that Ionotropin functions to maintain the normal, intracellular high levels of K^+ by regulating the NaK-ATPase. This process is necessary to compensate for the increased Na^+ diffusion caused by elevated levels of ENaC.

Feedback loop

Inadequate levels of glucocorticoid feedback on the hypothalamus to secrete CRF.

GH deficiency leads to excess secretion of corticosterone and inadequate synthesis of cortisol. The inadequate levels of cortisol lead to increased synthesis of CRF by the hypothalamus, thus completing the cycle (See figure 1).

Discussion

The new concepts presented in this paper are the role of corticosterone and Ionotropin. These two compounds complete the self-reinforcing endocrine cycle of PTSD. It is the self-reinforcing nature of the process that makes the disorder so long-lived. The lack of

REM sleep characteristic of patients with PTSD suggests that most are probably functionally GH deficient. This restricts 17α-hydroxylase activity and leads to increased corticosterone and decreased cortisol. As a consequence, corticosterone stimulates synthesis of ENaC, leading to Na^+ retention and K^+ wasting.

In brief, high levels of corticosterone lead to increased synthesis of ENaC. The elevated levels of ENaC increase passive diffusion of Na^+ and leads to potassium wasting. To compensate for the K^+ wasting, a patient with PTSD would need to synthesize Ionotropin, which, in turn, would cause hypertension. Until our discovery of Ionotropin, there were no known endogenous mammalian compounds that functioned as potassium sparing hormones.

Testing the hypothesis

There are several studies that could be used to test the hypothesis:

- Measure IGF-1 levels in a DSM-5 population confirmed to affected with PTSD.
- Evaluate REM sleep.
- Confirm elevated corticosterone to cortisol ratios, episodically and/or after ACTH administration.
- If testing confirms GH deficiency, consider a short course of rhGH or IGF1 therapy.
- If testing confirms high levels of corticosterone, consider a short course of a potent glucocorticoid.
- Consider implementation of a very low salt diet.

New approaches to therapy

- Choose drugs known to improve REM sleep, rather than anti-depressants.
- Amiloride and triamterene are K+ sparing diuretics that block synthesis of the ENaC response to mineralocorticoids. This therapy could reduce K+ wasting, decrease Ionotropin synthesis, and lead to lower blood pressures.
- Monitoring IGF-1 and/or Ionotropin levels might be useful markers to evaluate new therapies.

Conclusion

There are several endocrine problems commonly associated with PTSD. However, these problems are not independent. The recognition of the interrelation may provide a basis for improved diagnosis and therapy for PTSD. This hypothesis does not imply that all patients with PTSD have this trilogy. There may be multiple diseases that present with the PTSD DM-5 phenotype.

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Conflict of Interest

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