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Review Article

Neuro-Endocrinological Aspects of Borderline Personality Disorder: A Short Review

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Abstract

Hormones play a vital role in controlling different functions of a normal human body and slight changes in their levels in a body can greatly impact the ability of the body to function as normal. Various medical conditions are associated with a number of hormonal changes being the Borderline personality disorder (BPD), also known as emotionally unstable personality disorder (EUPD), is a long-term pattern of abnormal behavior characterized by unstable relationships with other people, unstable sense of self and unstable emotions. According to new research, many researchers agree that hormones can play a part in BPD. There is increasing evidence that the oxytocinergic system may be involved in affect dysregulation, behavioral dyscontrol, and interpersonal hypersensitivity and may thus contribute to borderline psychopathology and even open new avenues for targeted pharmacotherapeutic approaches. Because the intranasal administration of the neuropeptide oxytocin has been shown to improve facial recognition and to shift attention away from negative social information, the authors investigated whether borderline patients would benefit from oxytocin administration. When observing effects of sex hormones on BPD, as BPD is more pronounced in female gender, variation and not absolute levels of estrogen were seen to influence symptoms of BPD with relation to patients receiving OCPs also showed variations in BPD symptoms. Estrogen levels were seen to influence the serotonin system thus providing an evidence that any variation in estrogen might alter serotonin levels leading to mood disorders in BPD. When studying role of cortisol, enhancing effects of cortisol on memory retrieval of words was observed when comparing patients with controls. However there is evidence for HPA axis hyperactivity, reduced feedback sensitivity and enhanced cortisol excretion in BPD patients with evidence of feedback sensitivity to low-dose dexamethasone which can provide a possible therapeutic approach.

The aim of our review article is to demonstrate relationship and effects of certain hormones on BPD.

Keywords: *Borderline Personality Disorder (BPD); Hormones; Oxytocin; Estrogen; Ovarian Hormones; Cortisol; Therapy and Outcome*

Introduction

Borderline personality disorder (BPD), also known as emotionally unstable personality disorder (EUPD), is a long-term pattern of abnormal behavior characterized by unstable relationships with other people, unstable sense of self and unstable emotions. There is often dangerous behavior and self-harm. People may also struggle with a feeling of emptiness and a fear of abandonment. The behavior typically begins by early adulthood and occurs across a variety of situations. Substance abuse, depression, and eating disorders are com-

monly associated with BPD. As is the case with other mental disorders, the causes of BPD are complex and not fully agreed upon, it is believed that a history of childhood trauma can be a contributing factor, scientists have investigated the causal roles played by congenital brain abnormalities, genetics, neurobiological factors, and environmental factors other than trauma. Pathophysiology diagnosis of BPD.

The exact cause of BPD is unclear but seems to involve genetic, brain, environmental and social factors. It is about five times more prevalent in a person who has an affected first degree relative. It is noted that adverse life events such as emotional trauma also plays a role.

The underlying mechanism appears to involve the frontolimbic network of neurons. A number of neuroimaging studies in BPD have reported findings of reductions in regions of the brain involved in the regulation of stress responses and emotion, affecting the hippocampus, the orbitofrontal cortex, and the amygdala, amongst other areas. The hippocampus tends to be smaller in people with BPD, as it is in people with post-traumatic stress disorder (PTSD).

However, in BPD, unlike PTSD, the amygdala also tends to be smaller. The prefrontal cortex tends to be less active in people with BPD, Given its role in regulating emotional arousal, the relative inactivity of the prefrontal cortex explains the difficulties experienced in regulating the emotions and responses to stress in BPD patients [26]. Certain factors are held responsible for BPD but recent advances tells us about the role of certain hormones in BPD.

Oxytocin for example when given has shown to improve the trusting behavior and increased the facial recognition. It may decrease social threat hypersensitivity and thus reduce anger and aggressive behavior in borderline personality disorder [1-6]. Results from different studies show that fluctuation in estrogen level may influence the expression of borderline personality disorder as estrogen has been shown to be related to behavioral and cognitive patterns. BPD is more common among women and thus an influence of female hormones on the expression of associated symptoms is possible, but has not been empirically investigated [7,8,10,15]. The hypothalamic-pituitary-adrenal axis (HPA axis) regulates cortisol production, which is released in response to stress. Many studies have investigated the role of the hypothalamic-pituitary-adrenal (HPA) axis in post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). In BPD there is increasing evidence that alterations in HPA activity may contribute to the disorder thus altering the levels of cortisol and its negative- feedback mechanism. Cortisol production tends to be elevated in people with BPD, indicating a hyperactive HPA axis which might explain their greater vulnerability to irritability. It is strongly suggested that hormones do play a role in the pathophysiology of this disorder which is explained further in the text below [9,10,11-14,16-21].

There is no definitive medical test to diagnose BPD. BPD is best diagnosed by a mental health professional following a detailed clinical history that may include talking with previous clinicians, reviewing previous medical evaluations and, when appropriate, interviews with friends and family. A diagnosis is not based on one specific sign or symptom but as per the Diagnostic and Statistical Manual diagnostic framework, the main signs and symptoms may include [24]:

- Maniacal efforts to avoid abandonment by friends and family.
- Unstable personal relationships with splitting behavior that alternates between two extremes.
- Distorted self-image.
- Impulsive behaviors including self-harm that can have dangerous outcomes.
- Unstable moods, values, opinions and goals. Periods of intense depressed mood, irritability or anxiety lasting a few hours to a few days.
- Chronic feelings of boredom or emptiness.
- Uncontrollable anger followed by shame and guilt.
- Dissociative feelings, stress-related paranoid thoughts. Severe cases of stress can also lead to brief psychotic episodes.

Epidemiology

Borderline personality disorder contributes to 20 percent of psychiatric hospitalizations 10% of outpatients. The prevalence of BPD in a 2008 study was found to be 5.9% of the general population, occurring more often in women (6.2%) than in men (5.6%). These statistics are summarized in figure 1 and 2 [22].

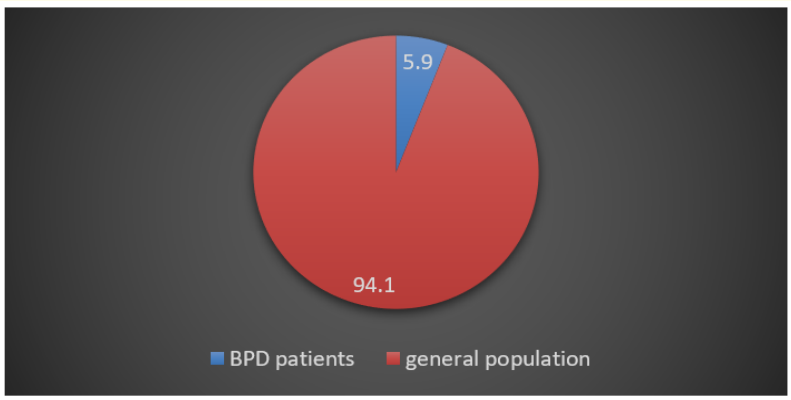

Figure 1: *Population distribution of borderline personality disorder among general population.*

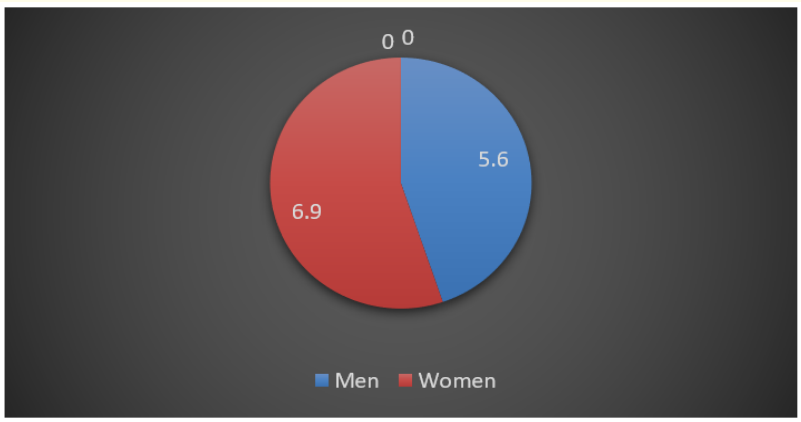

Figure 2: *Gender-based distribution of borderline personality disorder.*

Treatment and prevention of BPD

Currently Psychotherapy is the primary treatment for borderline personality disorder. Treatments should be based on the needs of the individual, rather than upon the general diagnosis of BPD. Cognitive behavioral therapy (CBT) is a type of psychotherapy used for treatment of BPD. This type of therapy relies on changing people's behaviors and beliefs by identifying problems from the disorder. It reduces anxiety and mood symptoms as well as reduces suicidal thoughts and self-harming behaviors. Also, mindfulness meditation may bring about favorable structural changes in the brain, including changes in brain structures that are associated with BPD. Medications are useful for treating comorbid disorders, such as depression and anxiety [23]. Antipsychotics and mood stabilizers are currently being used for treatment of BPD. Of the antipsychotics studied in relation to BPD, haloperidol may reduce anger, Olanzapine may decrease affective instability, anger, psychotic paranoid symptoms, and anxiety, and flupenthixol may reduce the likelihood of suicidal behavior. Of the mood stabilizers studied, Lamotrigine and topiramate may reduce impulsivity and anger. Valproate semisodium may eliminate depression,

interpersonal problems, and anger [24]. Proliferation knowledge and awareness of BPD among people and its prompt treatment is the base of prevention of this disorder. The Global Alliance for Prevention and Early Intervention for BPD had its origins at a meeting convened under the auspices of the National Education Alliance for BPD in New York in May 2014. The Alliance calls for action through a set of scientifically based clinical, research and social policy strategies and recommendations which include [25]:

1. Clinical priorities
    a) Early intervention.
    b) Training of mental health professionals.
    c) Indicated prevention.
    d) Early identification.
    e) The diagnosis of BPD should not be delayed.
    f) Misleading terms, or the intentional use of substitute diagnoses, should be discouraged.
2. Research priorities
    a) Prevention and early intervention for BPD with similar efforts for other severe mental disorders.
    b) Building a knowledge base for a health care system response to prevention and early intervention.
    c) Novel, low-cost preventive interventions that can be widely disseminated should be developed.
    d) Education and skill development programs.
    e) Further development and validation of brief and "user-friendly" assessment tools is needed
    f) Establishment detailed health economic data.
3. Social and policy priorities
    a) BPD needs to be recognized as a severe mental disorder.
    b) Evidence-based policy is needed to address BPD from primary through to specialist care.
    c) Discriminatory practices must be eliminated.

Review of Literature

Literature search strategy

A literature review was carried out to investigate the role of hormones in the borderline personality disorder. A medical search of literature was performed using the key words borderline personality disorder (BPD), hormones, oxytocin, estrogen, ovarian hormones, cortisol, therapy and outcome. Publications in Pub-Med and references from relevant articles published from 2002-2015 were analyzed.

As is the case with other mental disorders, the causes of BPD are complex and not fully understood. Researchers believe that a history of childhood trauma can be a major contributing factor in the development of the disease, but there are evidence of congenital brain abnormalities, genetics, neurobiological factors, and environmental factors other than trauma which play their part in disease development but less attention has been paid to investigating the causal roles played by them.

Hormone is a signaling molecules produced by glands-transported to target organs to regulate physiology and behavior. Thus behavior can be inferred based on hormone concentrations; hormone-release patterns; the numbers and locations of hormone receptors; and hormones can be interfered based on behavior so that a feedback mechanism is formed. It is possible that any influence of prenatal hormones on borderline personality may be driven primarily by an atypical sexual differentiation of brain regions integral to mood

and behavioral regulation (e.g. the amygdala and hypothalamus). This hypothesis is supported by researches showing that sex-specific patterns of activation occur in the amygdala following exposure to emotional stimuli and recent evidence that borderline personality is associated with an altered brain morphology in systems for emotional processing, including the amygdala [10].

Oxytocin and BPD

The neuropeptide oxytocin (OXT) has been shown to play a central role in pro-social behavior [10]. To study the role of oxytocin in BPD it was also noticed that the patients diagnosed with BPD specially women had a decreased levels of plasma OXT thus indicating a positive relationship of OXT with BPD [3]. Research indicates that OXT is critically involved in disunion distress, bond formation, affection, affinity and affiliation. For example, OXT, administered nasally, increased trusting behavior and improve facial recognition and shifts attention away from negative social information. OXT may thus be a useful agent to increase pro-social behavior in individuals who have difficulties with such behaviors like patients with BPD [1].

In a research carried out in which patients were given oxytocin intranasally suggests that the effects of OXT may differ in those with BPD. it was found that rather than having broad positive effects on social perception and behavior, OXT may increase the social cues, thereby activating the positive or negative emotions associated with them. The difference in the function of OXT suggest that effects of OXT on social perception and behavior may critically be moderated by individual differences especially differences in the relationship representations and expectations people possess.it is hypothesized that OXT system may be dysregulated in BPD which may lead to a differential response to exogenous OXT. Altered plasma OXT concentrations in women with BPD and a negative association between plasma oxytocin and BPD symptom severity may be considered as a first indicator for a dysregulation of the endogenous oxytocin system in BPD (Figure 3). Secondly it is believed that administration of exogenous OXT may activate chronic concerns about trust and closeness and increases the salience of social cues, or increases affiliative drive thus this may remind BPD participants of previous experiences where affiliation has gone wrong and activates their chronic concerns which leads to alteration in their pre-existing but maladaptive strategies to cope [1,6].

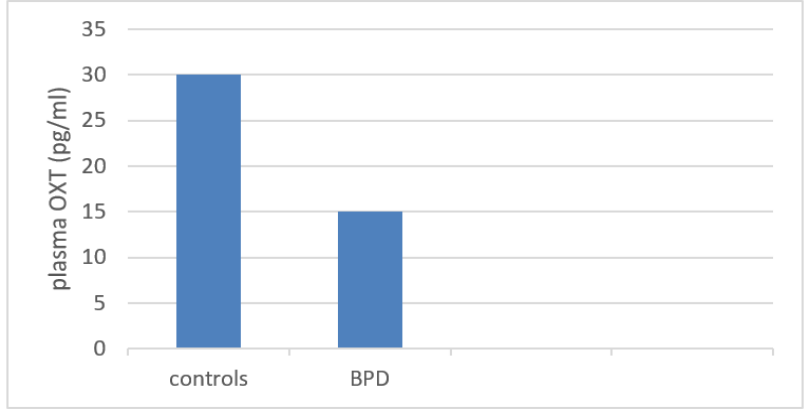

Figure 3: *Plasma Oxytocin levels in relation to BPD.*

However in another study there was a noticeable reduction of posterior amygdala hyperactivation, which was related to a reduced attentional bias toward socially threatening cues with faster eye movements in response to angry and fearful faces after oxytocin administration in borderline patients. Rapid and exaggerated eye movements toward the eyes of angry faces and a greater likelihood

of classifying predominantly happy faces as angry seem to be related to emotional hyperarousal in BPD, and hence it is one of the characteristics of this disorder that often leads to aggressive, self-injurious, or impulsive behaviors [2,5]. Furthermore studies were carried out which suggest that OXT administration affects emotional and neuroendocrine responses to psychosocial stress in BPD. Oxytocin's effect on the emotional response to stress is forewarned by a history of childhood trauma, while oxytocin's effect on the HPA axis response to stress is forewarned by insecure attachment. These diverging relationships may suggest a positive impact of OXT on emotion and HPA axis exists [4].

Role of sex hormones

According to research. BPD is three times more prevalent in women then in men. BPD symptoms were most common during times in the menstrual cycle when estrogen level is rising and in women using oral contraceptives. In relation with these two factors, Studies were perform on women and results suggest that rising or changing levels of estrogen may have more of an influence on BDP symptoms than absolute levels. First, BPD symptoms were more common in women assessed on cycle days during which estrogen generally rises relative to women assessed on other cycle days. Second, women using OCPs showed elevated BPD symptoms as compared with women not on OCPs [7,8]. another study hypothesize the role of progesterone along with estrogen in BPD suggesting that higher-than-usual progesterone during the luteal phase: (1) periods of relatively lower luteal Estrogen that occur following ovulation and during the few days preceding the onset of menses are associated with increased risk for BPD symptom expression, whereas (2) periods of relatively higher luteal Estrogen (i.e. during mid-luteal phase) are associated with very low levels of BPD symptoms [8]. A study also suggested a relationship between BPD and PCO. Patients with BPD had significantly increased serum androgen concentrations which lead to development of PCOs. Furthermore, Disturbed glucose metabolism in BPD patients leads to elevated ovarian insulin concentration facilitating intraovarian hyperandrogenism, which contributes to the arrest of follicular maturation characteristic of PCOS thus constituting a vicious cycle [15].

One potential link between estrogens and BDP is the serotonin system. Serotonin and the principal metabolite of serotonin, 5-HIAA, are higher during high estrogen phases of the cycle thus it is possible that changes in estrogen levels, influence these systems and the expression of BDP. Furthermore, in a separate study comparing the role of serotonin with impulsivity and aggression in male patients with personality disorders also suggested reduced levels of serotonin in subjects with BPD thus emphasizing on positive relationship of serotonin with BPD [7,9].

Cortisol and BPD

There is preceding evidence that the hypothalamic-pituitary-adrenal (HPA) axis is normally responsible for behavioral and physiological regulation of stress. In BPD the HPA shows increased/abnormal activity due to an enhanced corticotropin-releasing hormone (CRH) drive and glucocorticoid feedback resistance, leading to problems in stress resiliency and emotional regulation [13,14].

In a study evaluating the role of cortisol in relation to parental protection in female BPD subjects suggests that the daughter's perception of protection in the mother-child relationship was significantly lower for young adults with BPD and these perceptions of lack of protection were accompanied by elevated cortisol seen during the recovery period in the anticipation of a conflict discussion. The conflict discussion appears to be a specific stressor for BPD subjects, because the healthy subjects showed a low level of cortisol during the study period with an initial higher cortisol concentration. Secondly, higher levels of overall cortisol in subjects with BPD were found compared to non-BPD controls. These results confirm the hypothesis that those with BPD show elevated cortisol levels in the anticipation of a conflict discussion.it is safe to hypothesize that prolonged or excessive activation of the HPA axis would lead to the development of hypo-responsiveness and that, therefore, chronic psychological stress in BPD patients might lead to attenuated cortisol release due to adrenal hypofunction or to alterations in suprapituitary pathways [12,13,17]. To further evaluate the role of cortisol, measurement of diurnal salivary cortisol secretion appeared a suitable approach to assess basic functions of HPA-axis activity in BPD

patient during natural, non-laboratory conditions. Measurements on two consecutive days (days 1 and 2) showed consistently increased cortisol secretion and lowered feedback sensitivity to low-dose dexamethasone. These findings were consistent with the study performed by Wingenfeld and colleagues who investigated overnight urinary free cortisol in patients with BPD compared to controls. However on day 3 of diurnal salivary cortisol study, dexamethasone administration showed a fall in cortisol secretion of both BPD and controls (Figure 4). Increased cortisol levels in BPD patients might result from current life-time stress. Experimental studies clearly demonstrate that central stress coping mechanisms fail within this group of patients and patients with BPD suffer from recurrent states of severe inner tension and dissociation [11,16,18].

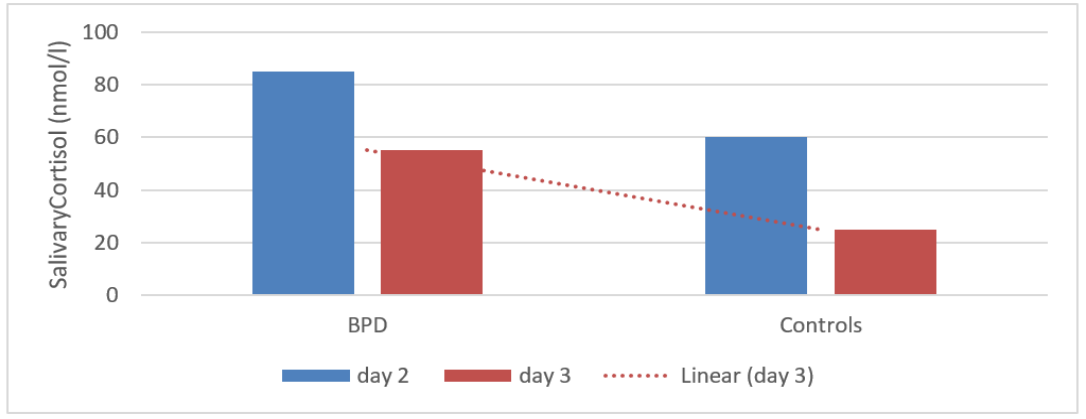

Figure 4: *Effect of 0.5 mg dexamethasone on cortisol levels in 23 patients with BPD and 24 healthy controls. Linear line indicates significant suppression of cortisol secretion in both patients and controls.*

Recent animal studies tells us that when rat infants were deprived from maternal care it led to an enhanced CRH or arginine vasopressin (AVP) drive from the hypothalamus, an enhanced glucocorticoid response to stress, and altered expression of glucocorticoid and mineralocorticoid receptors in the brain. Several studies have demonstrated a much more potent suppression of the HPA axis by the synthetic glucocorticoid-dexamethasone compared with healthy control subjects in patients with stress disorders (Figure 2). However, there is decreased efficacy of dexamethasone suppression associated with Major Depressive Disorder in the investigated BPD population. However there is convincing evidence available for BPD patients without any comorbid for hypersensitive response to the dexamethasone test. A study shows that 64% BPD patients were cortisol suppressors in the test versus only 20% patients with other personality disorders [12,14,21].

On the other hand, positive effects of exogenous cortisol were notices on declarative memory tasks in BPD patients, in contrast to healthy controls. Cortisol had enhancing rather than impairing effects on memory retrieval. A similar effect was seen in the working memory task but only when negative interference words were presented. BPD patients show hippocampal dysfunctions but a more pronounced GR sensitivity, resulting in a state where effects of cortisol turn beneficial. It has been suggested that GR mediate the impairing effects of cortisol, while MR along with a moderate GR occupation might facilitate hippocampal function [19,20].

Conclusion

Psychotherapy is recommended as the primary treatment for the disorder. Currently available pharmacological treatments for BPD are of modest efficacy and primarily target the impulsive aggression, affective instability, and psychoticism. As OXT has been shown to

reduce social anxiety and increase social abilities in animal and human studies its therapeutic use warrants further research, as it might be an important target for therapeutic approaches in several mental disorders that are characterized by social interaction pathology.

According to research, variation and not absolute levels of estrogen influence symptoms of BPD. Results of these studies suggest that extreme fluctuations in estrogen may be troublesome, or that normal fluctuations are problematic for women with high pre-existing levels of BPD symptomology. These fluctuations in estrogen levels influence serotonin system sensitivity. Furthermore study supports the hypothesis that the use of OCPs may cause an increase in BPD symptoms but only among women who have increasing BPD tendencies. Although studies provides useful information about how ovarian hormones effect BPD features in at-risk women, further experimental studies therefore will be necessary to make causal inferences regarding the pathophysiological role of hormone deviations in BPD feature expressions keeping in mind the role of estrogen and progesterone on biological cholinergic, dopaminergic, adrenergic and serotonergic pathways.

Continual stress can lead to high levels of circulating cortisol, which can create an allostatic load which leads to various physical modifications in the body's regulatory network. Altered patterns of serum cortisol levels have been observed in connection with mood disorders, psychological stress, and physiological stressors. In total, there is evidence for HPA axis hyperactivity, reduced feedback sensitivity and enhanced cortisol excretion in BPD patients. These alterations were mediated by depressive psychopathology and trauma related features of BPD. Few studies reliably demonstrate that patients with BPD show increased cortisol secretion and lowered but up to some extant feedback sensitivity to low-dose dexamethasone which can effectively we used therapeutically after control trials [21]. Future studies should be performed to investigate the effect of enhanced quality of parental protectiveness on emotional regulation and stress resiliency among young adults with BPD. Furthermore it is necessary to evaluate that whether or not the beneficial role of cortisol on memory in BPD group is superior to its adverse effects on the mood and personality of BPD patients.

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