Aggressive behavior in psychiatric patients in relation to hormonal imbalance (Review)

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Abstract. Aggressive behavior is one of the main characteristics of different psychiatric disorders such as: personality disorders (antisocial personality disorder, borderline personality disorder), schizophrenia, intermittent explosive disorder, post-traumatic stress disorder, bipolar disorder, depression, alcohol/substance induced psychiatric disorders. Epidemiological evidence shows that always there is a higher risk of violence and aggressivity among patients with psychiatric disorders compared with general population. Researchers have tried many times to narrow the theories that can explain such a behavior, starting from models that involve a link between illness and aggression going up to external-environmental factors including the therapeutic relation in the hospital. Even if the majority of studies are centered on intoxications (with alcohol or other substances that potentiate the aggressive behavior) we will highlight another somatic dimension linked with this behavior. In the following review we summarize the hormonal imbalances that have been noted to accompany aggressive behavior in different psychiatric disorders. Several studies have been made starting even at the age of ten correlating hormone cortisol with increase aggression, but patients with psychiatric disorders have a higher sensitivity in linking hormonal imbalance with their behavior.

Contents
1. Introduction
2. Cortisol and testosterone
3 Vasopressin
4. Thyroid hormones
5. Serotonin
6. Catecholamines
7. Conclusion

1. Introduction

In the psychiatry department aggressive behavior can be seen in a significant number of patients regardless of their diagnosis. Whether they display a hetero-aggressive or an auto-aggressive behavior, most patients describe a lack of self-control in particular situations. This is a major public health risk, violent behavior being at the root of criminal offences. A multitude of pathophysiological imbalances can be the cause of aggressive behaviour in these patients. Moreover, suicidal behavior shares certain neurobiological aspects with aggressive behavior (1). For example, hetero-aggressive behaviour might be a consequence of auditory hallucinations, of disinhibition due to bipolar disorder or a characteristic of a personality disorder. This review presents the hormonal aspects that are observed in patients with mental health diagnostics that display aggressive behavior.

The central nervous system and the endocrine system, intertwined, are responsible for homeostasis and responsivity to stimuli. This interconnection is our ancestral heritage and it is the interface we use to interact with the outside world since the beginning of time. A number of psychiatric diseases can be accompanied by disruption of the normal hormonal balance (caused by the disease itself or by the prescribed medication). Conversely, patients with endocrine pathologies can manifest psychiatric symptoms (2).

2. Cortisol and testosterone

The hypothalamus-pituitary-adrenal (HPA) axis and the hypothalamus-pituitary-gonadal (HPG) axis are two key endocrine components that work together in enabling a person to withdraw himself in the presence of threatening stimuli and persevere at the sight of a rewarding stimuli. The end products of those two circuits, cortisol and testosterone, are linked to aggressive behavior.
Cortisol is thought to enhance fearfulness and withdrawal behavior in the amygdala (3), whereas testosterone is responsible for reward-seeking behavior (4). Another study revealed that, through negative feedback, cortisol levels may diminish the level of testosterone by suppressing the HPG axis at all its levels (5). Moreover, it was proven that testosterone inhibits the activation of HPA axis mediated by stress at the level of the hypothalamus (6). It is supposed that if an imbalance which raises the testosterone level occurs in the amygdala the person will become more aggressive. A study concluded that psychopathy and aggressive behavior are related only to high ratio of testosterone to cortisol levels. Lower levels of testosterone have a minimal effect on the amygdala and the ratio of testosterone to cortisol has less impact on behavior (7). It was also postulated that lower levels of testosterone are a protective factor against antisocial behavior or for postpartum women that actually reported fewer symptoms of depression due to the fathers’ postpartum depression (8).

The general consensus regarding aggression mediated by cortisol and testosterone has divided the population of aggressors into two main categories: hypoarousal-driven aggressiveness and hyperarousal-driven aggression.

Hypoarousal aggression is seen in antisocial personality disorder and in conduct disorder in children (9). This category is defined by low cortisol plasmatic levels, reduced adrenalin reaction to stress and diminished basal heart rate (10). The hypoarousal theory is supposed to be an adaptive mechanism which removes the emotional barrier that may question the violent behavior (11).

Hyperarousal aggression is observed in both intermittent explosive disorder and depression (in sudden outbursts of aggression) (12,13). This type of aggression is accompanied by acute exaggerated glucocorticoid response to stress (14), increased automatic arousal and emotional reactions (anger). In addition, hyperarousal can be seen in chronic burnout and post-traumatic stress disorder patients and is a component of their irritable aggression (15,16).

The role of testosterone in the pathophysiology of aggression is controversial. While it is considered the main androgenic hormone to promote aggressive behavior (17), its exact role is not fully known. Testosterone is considered to be both the cause of aggressive behavior and the effect of establishing dominance through aggressive means (18). It was long proven that chemical castration with gonadotropin release hormone (GnRH) reduces aggressiveness and testosterone levels (19). Also, it was documented that testosterone levels rose after winning and establishing dominance (20). Studies suggested that atypical exposure to testosterone (especially prenatal) may predispose to aggressive behavior, this effect being greater in girls (21).

Studies conducted on violent criminals showed much higher testosterone levels in personality disordered criminals than in criminals diagnosed with schizophrenia (22). Controversially, one study found that low to normal testosterone levels were associated with symptoms of hostility in men with schizophrenia (23). Furthermore, a series of studies reported that men diagnosed with schizophrenia had lower levels of plasmatic testosterone throughout acute psychotic episodes (24,25). The reduction in testosterone level may be due to antipsychotic medication, but a study replicated the results in naïve non-medicated schizophrenic patients (26).

There are a number of studies that describe a relationship between testosterone levels and suicide attempts (27). One study determined that the testosterone level of men that attempted violent suicide was lower than of men who attempted non-violent suicide, schizophrenic patients that had suicidal attempts ranging at even lower testosterone plasmatic level (28). In a study conducted on patients with bipolar disorder there was a direct correlation between the testosterone level and the number of suicide attempts (29).

Cortisol levels vary among psychiatric patients and there have been a number of studies that describe a relationship between elevated cortisol levels and suicide attempts. One study concluded that bipolar patients with suicide attempts had higher levels of plasmatic cortisol, the correlation being even stronger among those who had serious suicide attempts (30). Another study observed a strong relation between hyperactivity of the HPA-axis (certified by baseline abnormal dexamethasone suppression test) and attempted suicide or completed suicide in depressed patients. The hyperactivity was viewed as an additive risk for suicide in those patients (31).

3. Vasopressin

Studies suggest there is a positive association between aggression and impulsivity and plasmatic levels of vasopressin (32). In personality disordered patients there was a positive correlation between vasopressin level in the cerebral spinal fluid and personal history of aggression (33).

A study conducted on depressed people correlated the concentration of vasopressin in the cerebral spinal fluid and cortisol (34).

4. Thyroid hormones

Thyroid disorders are generally more common in women than in men. Most of the time, women ignore the symptoms, considering them due to other conditions (menopause or depression). There is also an increased risk of thyroid disease after pregnancy. Similarly, the thyroid gland may release excess thyroid hormones (hyperthyroidism) or in an insufficient amount (hypothyroidism).

Thyroid function and psychiatric disorders, especially mood disorders, are proved to be correlated. Historically, this association dates more than 200 years. One of the first cases, documented in 1825, presents an increased incidence of ‘nervous affections’ in thyroid disorders. Later, in 1873, studies showed the relation between myxedema and psychosis that was confirmed in 1888 by the Committee of the Clinical Society. Another case was mentioned in 1949, where the term ‘myxedema madness’ was used to describe the mental state of subjects with hypothyroidism (35).

In adults, the effect of thyroid dysfunction on mental and brain functions is less defined. However, mood disorders and decreased quality of life are consequences for hyperthyroid patients, also after restoration of euthyroidism. Furthermore, psychiatric diseases are known to be developed by the interaction of thyroid hormones with serotonin and norepinephrine, both neurotransmitters. This states a plausible link between hyperthyroidism and psychiatric morbidity (36).
Studies point out that the frontal lobe is responsive to thyroid hormone, discovered with the help of magnetic resonance spectroscopy (MRS) and positron emission topography (37). This provides a biological basis for the prevalent neurological and psychiatric signs found in hypothyroidism (38). The wide variety of neuropsychiatric symptoms associated with hypothyroidism includes impaired cognition, mood changes, irritability and psychosis (39).

Numerous studies suggest that there is a strong relation between high plasmatic T3 levels and the tendency to commit a crime (40). A study conducted on prisoners with antisocial personality disorder determined that they had elevated plasmatic levels of free T4 and cortisol, while free T3 level was significantly lower (41). However, a follow-up study concluded a high correlation between high levels of T3 and irritability and detachment in violent criminal recidivists (42).

A study reported that high aggression scores are associated with low T3/T4 ratio in suicide attempts (43).

5. Serotonin

It is well known that serotonin has inhibitory control regarding impulsive aggression (44). A series of experimental studies concluded that there is a reduction of serotonin's metabolite 5-hydroxy-indoleacetic acid (5-HIAA) in persons with personality disorders that have a lifetime history of aggressiveness (45,46).

Type 2 alcoholics are well known for their aggressive behavior. Interestingly, this type is associated with reduction in serotonergic activity (47). An association between a low-activity serotonin transporter genotype and alcoholism with violent behavior was reported (48).

Also, it was hypothesized that self-mutilating and auto-aggressive behavior is associated with serotonin depletion in the central nervous system (49). Numerous publications validated the hypothesis linking serotonin reduction to hetero-aggressive and auto-aggressive behavior (50,51). This theory is also supported by the fact that selective serotonin reuptake inhibitors (SSRIs) reduce aggressive behavior (52). A study conducted on patients with intermittent explosive disorder demonstrated a reduced serotonin activity in the orbital prefrontal cortex and ventral medial cortex (53). A postmortem study conducted on suicide victims that suffered from borderline personality disorder revealed an increase in post-synaptic 5-HT(2A) receptor binding in the hippocampus of those patients. This finding reiterates the fact that dysregulations of the serotonergic activity may be a cause of the behavioral changes in borderline personality disorder (54).

6. Catecholamines

Catecholaminergic synapses can be found throughout the central nervous system and there is growing evidence that those circuits are involved in regulation of aggressive behavior. Norepinephrine and dopamine decrease the threshold of violent response to external stimuli (55).

Monoamine-oxidase (MAO) and catechol-O-methyltransferase (COMT) are the two enzymes responsible for degradation of norepinephrine. The metabolic regulation of norepinephrine has been linked to aggressive behavior. Low MAO activity was observed in relation to violent criminals with a history of personality disorders (56). Several studies revealed a predisposition to aggressive behavior in schizophrenic patients that had an allele coding a less active form of the COMT enzyme (57,58). Also this allele was associated with violent suicidal attempts among schizophrenic patients (59). A study found a high correlation between COMT activity and severity of manic symptoms in patients suffering from bipolar disorder (60).

Dopaminergic circuits located in the meso-corticolimbic system are involved in the executive functions that generate aggressive behavior (61). Using positron emission tomography, it was revealed that decreased D1 receptors were present in patients with depression and anger attacks (62).

A few studies were conducted to assess the dopaminergic system by measuring the level of growth hormone (GH) after administering apomorphine. Apomorphine stimulates the GH response by D2 receptors (63,64). Data collected on depressed patients supported the hypothesis that the reduction of dopamine might be in relation to the biology of suicide in those patients (65). Also, the results were replicated on non-depressed patients with a history of suicidal attempts (66).

7. Conclusion

Being a neuromodulator, neuronal and glial development is essentially regulated by serotonin. It acts as a signal of development. Many psychiatric disorders are linked to the serotonergic system. The serotonergic system also predominates on the etiopathogenesis of two important endophenotypes: impulsivity and aggression. The aggression phenomenon has been highlighted through an increase of 5HT2A receptor concentration in orbital prefrontal cortex.

There are still unknown key components of the pathophysiological mechanisms of aggression. In the psychiatric patients the gap of knowledge is even greater. The unknown elements render the clinical psychiatrist vulnerable to the aggression that might unravel before him. This review aims to present possible areas of research that might close the gap for better understanding of the troubled mind. Treatments that combine hormonal therapy might be the future for aggressive psychiatric patients, but the prospects have to be carefully analyzed and documented.

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Competing interests

The authors declare that they have no competing interests.

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