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 corelating hormone cortisol with increase aggression, but patients with psychiatric disorders have a higher sensitivity in linking hormonal imbalance with their behavior.

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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 affectations’ 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 provide 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 serotoninergic 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 frontal cortex and ventral medial cortex (53). A post-mortem 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 serotoninergic 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 maniac 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.

References

1. Volavka J (ed): Neurobiology of Violence. 2nd edition. American Psychiatric Association Publishing, Washington, DC, 2002.
2. Roh JW, Park HJ and Kang UG: Hormones and psychiatric disorders. Clin Psychopharmacol Neurosci 5: 3-13, 2007.
3. Schulkin J, Gold PW and McEwen BS: Induction of corticotropin-releasing hormone gene expression by glucocorticoids: Implication for understanding the states of fear and anxiety and allostatic load. Psychoneuroendocrinology 23: 219-243, 1998.
4. Daitzman R and Zuckerman M: Disinhibitory sensation seeking, personality and gonadal hormones. Pers Individ Dif 1: 103-110, 1980.
5. Tilbrook AJ, Turner AI and Clarke IJ: Effects of stress on reproduction in non-rodent mammals: The role of glucocorticoids and sex differences. Rev Reprod 5: 105-113, 2000.
6. Williamson M and Viau V: Selective contributions of the medial preoptic nucleus to testosterone-dependent regulation of the paraventricular nucleus of the hypothalamus and the HPA axis. Am J Physiol Regul Integr Comp Physiol 295: R1020-R1030, 2008.
7. Glenn AL, Raine A, Schug RA, Gao Y and Granger DA: Increased testosterone-to-cortisol ratio in psychopathy. J Abnorm Psychol 120: 389-399, 2011.
8. Trifu S, Vladuti A and Popescu A: Neuroendocrine aspects of pregnancy and postpartum depression. Acta Endocrinol (Bucur) 15: 410-415, 2019.
9. Vanyukov MM, Moss HB, Plail JA, Blackson T, Mezzich AC and Tarter RE: Antisocial symptoms in preadolescent boys and in their parents: Associations with cortisol. Psychiatry Res 46: 9-17, 1993.
10. Brennan PA, Raine A, Schulsinger F, Kirkegaard-Sorensen L, Knop J, Hutchings B, Rosenberg R and Mednick SA: Psychophysiological protective factors for male subjects at high risk for criminal behavior. Am J Psychiatry 154: 853-855, 1997.
11. Raine A: Autonomic nervous system factors underlying disinhibited, antisocial, and violent behavior. Biosocial perspectives and treatment implications. Ann N Y Acad Sci 794: 46-59, 1996.
12. Trifu S and Gutt A: Interpretative process - from utilization of predominant to psychotic decompensation. Procedia Soc Behav Sci 187: 429-433, 2015.
13. Olvera RL: Intermittent explosive disorder: Epidemiology, diagnosis and management. CNS Drugs 16: 517-526, 2002.
14. Haller J, Mikics E, Halász J and Tóth M: Mechanisms differentiating normal from abnormal aggression: Glucocorticoids and serotonin. Eur J Pharmacol 526: 89-100, 2005.
15. Trifu S: Neuroendocrine insights into burnout syndrome. Acta Endocrinol (Bucur) 15: 404-405, 2019.
16. Southwick SM, Bremner JD, Rasmusson A, Morgan CA III, Arnsten A and Charney DS: Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biol Psychiatry 46: 1192-1204, 1999.
17. Giammanco M, Tabacchi G, Giammanco S, Di Majo D and La Guardia M: Testosterone and aggressiveness. Med Sci Monit 11: RA136-RA145, 2005.
18. Pope HG Jr, Kouri EM and Hudson JI: Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: A randomized controlled trial. Arch Gen Psychiatry 57: 133-140, discussion 155-156, 2000.
19. Loosen PT, Purdon SE and Pavlou SN: Effects on behavior of modulation of gonadal function in men with gonadotropin-releasing hormone antagonists. Am J Psychiatry 151: 271-273, 1994.
20. Zilioli S and Watson NV: Testosterone across successive competitions: Evidence for a 'winner effect' in humans? Psychoneuroendocrinology 47: 1-9, 2014.
21. Ramirez JM: Hormones and aggression in childhood and adolescence. Aggress Violent Behav 8: 621-644, 2003.
22. Räsänen P, Hakko H, Visuri S, Paanila J, Kapanen P, Suomela T and Tiihonen J: Serum testosterone levels, mental disorders and criminal behaviour. Acta Psychiatr Scand 99: 348-352, 1999.
23. Moore L, Kyaw M, Vercammen A, Lenroot R, Kulkarni J, Curtis J, O'Donnell M, Carr VJ, Shannon Weickert C and Weickert TW: Serum testosterone levels are related to cognitive function in men with schizophrenia. Psychoneuroendocrinology 38: 1717-1728, 2013.
24. Taherianfard M and Shariaty M: Evaluation of serum steroid hormones in schizophrenic patients. Indian J Med Sci 58: 3-9, 2004.
25. Huber TJ, Tettenborn C, Leifke E and Emrich HM: Sex hormones in psychotic men. Psychoneuroendocrinology 30: 111-114, 2005.
26. Fernandez-Egea E, García-Rizo C, Miller B, Parellada E, Justicia A, Bernardo M and Kirkpatrick B: Testosterone in newly diagnosed, antipsychotic-naive men with nonaffective psychosis: A test of the accelerated aging hypothesis. Psychosom Med 73: 643-647, 2011.
27. Markianos M, Tripodianakis J, Istikoglou C, Rouvali O, Christopoulos M, Papageorgopoulos P and Seretis A: Suicide attempt by jumping: A study of gonadal axis hormones in male suicide attempters versus men who fell by accident. Psychiatry Res 170: 82-85, 2009.
28. Tripodianakis J, Markianos M, Rouvali O and Istikoglou C: Gonadal axis hormones in psychiatric male patients after a suicide attempt. Eur Arch Psychiatry Clin Neurosci 257: 135-139, 2007.
29. Sher L, Grunebaum MF, Sullivan GM, Burke AK, Cooper TB, Mann JJ and Oquendo MA: Testosterone levels in suicide attempters with bipolar disorder. J Psychiatr Res 46: 1267-1271, 2012.
30. Kamali M, Saunders EF, Prossin AR, Brucksch CB, Harrington GJ, Langenecker SA and McInnis MG: Associations between suicide attempts and elevated bedtime salivary cortisol levels in bipolar disorder. J Affect Disord 136: 350-358, 2012.
31. Coryell W, Young E and Carroll B: Hyperactivity of the hypothalamic-pituitary-adrenal axis and mortality in major depressive disorder. Psychiatry Res 142: 99-104, 2006.
32. Albers HE: The regulation of social recognition, social communication and aggression: Vasopressin in the social behavior neural network. Horm Behav 61: 283-292, 2012.
33. Coccaro EF, Kavoussi RJ, Hauger RL, Cooper TB and Ferris CF: Cerebrospinal fluid vasopressin levels: Correlates with aggression and serotonin function in personality-disordered subjects. Arch Gen Psychiatry 55: 708-714, 1998.
34. Brunner J, Keck ME, Landgraf R, Uhr M, Namendorf C and Bronisch T: Vasopressin in CSF and plasma in depressed suicide attempters: Preliminary results. Eur Neuropsychopharmacol 12: 489-494, 2002.
35. Gutman DA and Nemeroff CB: Neuroendocrinology. In: Biological Psychiatry. D'Haenen H, Boer JAD and Willner P (eds). John Wiley & Sons, Chichester, pp97-110, 2002.
36. Bunevicius R and Prange AJ Jr: Thyroid disease and mental disorders: Cause and effect or only comorbidity? Curr Opin Psychiatry 23: 363-368, 2010.
37. Smith CD and Ain KB: Brain metabolism in hypothyroidism studied with 31P magnetic-resonance spectroscopy. Lancet 345: 619-620, 1995.
38. Dugbartey AT: Neurocognitive aspects of hypothyroidism. Arch Intern Med 158: 1413-1418, 1998.
39. Bauer M, Heinz A and Whybrow PC: Thyroid hormones, serotonin and mood: Of synergy and significance in the adult brain. Mol Psychiatry 7: 140-156, 2002.
40. Eklund J, Alm PO and af Klinteberg B: Monoamine oxidase activity and tri-iodothyronine level in violent offenders with early behavioural problems. Neuropsychobiology 52: 122-129, 2005.
41. Evrensel A, Ünsalver BÖ and Özşahin A: The relationship between aggression and serum thyroid hormone level in individuals diagnosed with antisocial personality disorder. Noro Psikiyatri Arsivi 53: 120-125, 2016.

42. Stalenheim EG: Long-term validity of biological markers of psychopathy and criminal recidivism: Follow-up 6-8 years after forensic psychiatric investigation. Psychiatry Res 121: 281-291, 2004.
43. Sinai C, Hirvikoski T, Vansvik ED, Nordström AL, Linder J, Nordström P and Jokinen J: Thyroid hormones and personality traits in attempted suicide. Psychoneuroendocrinology 34: 1526-1532, 2009.
44. Trifu S: Dissociative identity disorder. Psychotic functioning and impairment of growing-up processes. J Educ Sci Psychol 9: 102-108, 2019.
45. Siever L and Trestman RL: The serotonin system and aggressive personality disorder. Int Clin Psychopharmacol 8 (Suppl 2): 33-39, 1993.
46. Winstanley CA, Theobald DE, Dalley JW, Glennon JC and Robbins TW: 5-HT2A and 5-HT2C receptor antagonists have opposing effects on a measure of impulsivity: Interactions with global 5-HT depletion. Psychopharmacology (Berl) 176: 376-385, 2004.
47. Virkkunen M and Linnoila M: Serotonin in early-onset, male alcoholics. In: Recent Developments in Alcoholism. Galanter M (ed). Springer, Boston, MA, pp173-189, 2005.
48. Hallikainen T, Saito T, Lachman HM, Volavka J, Pohjalainen T, Ryynänen OP, Kauhanen J, Syvälahti E, Hietala J and Tiihonen J: Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. Mol Psychiatry 4: 385-388, 1999.
49. New AS, Trestman RL, Mitropoulou V, Benishay DS, Coccaro E, Silverman J and Siever LJ: Serotonergic function and self-injurious behavior in personality disorder patients. Psychiatry Res 69: 17-26, 1997.
50. Siever LJ: Neurobiology of aggression and violence. Am J Psychiatry 165: 429-442, 2008.
51. Reif A, Rösler M, Freitag CM, Schneider M, Eujen A, Kissling C, Wenzler D, Jacob CP, Retz-Junginger P, Thome J, *et al*: Nature and nurture predispose to violent behavior: Serotonergic genes and adverse childhood environment. Neuropsychopharmacology 32: 2375-2383, 2007.
52. Coccaro EF and Kavoussi RJ: Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. Arch Gen Psychiatry 54: 1081-1088, 1997.
53. Siever LJ, Buchsbaum MS, New AS, Spiegel-Cohen J, Wei T, Hazlett EA, Sevin E, Nunn M and Mitropoulou V: d,l-fenfluramine response in impulsive personality disorder assessed with [18F]fluorodeoxyglucose positron emission tomography. Neuropsychopharmacology 20: 413-423, 1999.
54. Soloff PH, Price JC, Meltzer CC, Fabio A, Frank GK and Kaye WH: 5HT2A receptor binding is increased in borderline personality disorder. Biol Psychiatry 62: 580-587, 2007.
55. Volavka J, Bilder R and Nolan K: Catecholamines and aggression: The role of COMT and MAO polymorphisms. Ann N Y Acad Sci 1036: 393-398, 2004.
56. Belfrage H, Lidberg L and Oreland L: Platelet monoamine oxidase activity in mentally disordered violent offenders. Acta Psychiatr Scand 85: 218-221, 1992.
57. Strous RD, Nolan KA, Lapidus R, Diaz L, Saito T and Lachman HM: Aggressive behavior in schizophrenia is associated with the low enzyme activity COMT polymorphism: A replication study. Am J Med Genet B Neuropsychiatr Genet 120B: 29-34, 2003.
58. Singh JP, Volavka J, Czobor P and Van Dorn RA: A meta-analysis of the Val158Met COMT polymorphism and violent behavior in schizophrenia. PLoS One 7: e43423, 2012.
59. Nolan KA, Volavka J, Czobor P, Cseh A, Lachman H, Saito T, Tiihonen J, Putkonen A, Hallikainen T, Kotilainen I, *et al*: Suicidal behavior in patients with schizophrenia is related to COMT polymorphism. Psychiatr Genet 10: 117-124, 2000.
60. Bortolato M, Walss-Bass C, Thompson PM and Moskovitz J: Manic symptom severity correlates with COMT activity in the striatum: A post-mortem study. World J Biol Psychiatry 18: 247-254, 2017.
61. de Almeida RM, Ferrari PF, Parmigiani S and Miczek KA: Escalated aggressive behavior: Dopamine, serotonin and GABA. Eur J Pharmacol 526: 51-64, 2005.
62. Dougherty DD, Bonab AA, Ottowitz WE, Livni E, Alpert NM, Rauch SL, Fava M and Fischman AJ: Decreased striatal D1 binding as measured using PET and [$_{11}$C]SCH 23,390 in patients with major depression with anger attacks. Depress Anxiety 23: 175-177, 2006.
63. Pitchot W, Hansenne M, Moreno AG and Ansseau M: Suicidal behavior and growth hormone response to apomorphine test. Biol Psychiatry 31: 1213-1219, 1992.
64. Pitchot W, Hansenne M, Gonzalez Moreno A, Pinto E, Reggers J, Fuchs S, Pirard S and Ansseau M: Reduced dopamine function in depressed patients is related to suicidal behavior but not its lethality. Psychoneuroendocrinology 26: 689-696, 2001.
65. Pitchot W, Reggers J, Pinto E, Hansenne M, Fuchs S, Pirard S and Ansseau M: Reduced dopaminergic activity in depressed suicides. Psychoneuroendocrinology 26: 331-335, 2001.
66. Pitchot W, Hansenne M and Ansseau M: Role of dopamine in non-depressed patients with a history of suicide attempts. Eur Psychiatry 16: 424-427, 2001.