



Aggression: The Testosterone-Serotonin Link

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Abstract

The relevance of central neurotransmission to aggressive and impulsive behavior has become more evident due to extensive research in humans and animals. Among other findings, there are abundant data relating low serotonergic activity – as measured by low cerebrospinal fluid 5-hydroxyindolacetic acid, and a blunted response of prolactin to fenfluramine – to impulsive behavior. Many studies on testosterone activity show a relation between high plasma levels and a tendency towards aggression. It is hypothesized that the interaction between low serotonin and high testosterone levels in the central nervous system has a significant effect on the neural mechanisms involved in the expression of aggressive behavior. It seems that testosterone modulates serotonergic receptor activity in a way that directly affects aggression, fear and anxiety. Our survey reviews the main findings on serotonin, testosterone and the possible interaction between them with regard to these behavioral phenomena.

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Aggression is a complex social behavior with many definitions. The most suitable for clinical implications is that proposed by Moyer [1]: "An overt behavior with the intention of inflicting damage or other unpleasantness upon another individual." Aggression may occur in a broad spectrum of human behaviors ranging from an episodic, normal reaction to more generalized, pervasive manifestations in severe psychopathologies. In both humans and animals, the term aggression comprises behaviors that are non-homogenous for clinical phenomenology and neurobiologic features, making simple extrapolation from animal subtypes to humans not feasible. Nonetheless, clinical observations, experimental laboratory paradigms and cluster/factor-analytic statistics have been used in attempts to subdivide aggression in both humans and animals, thus broadening our understanding of the similar and non-similar factors that underlie aggression [2]. Violence has been defined as the physical force exerted for the purpose of violating, damaging, or abusing [3].

In humans, aggressive antisocial behavior, which is a complex phenomenon, is defined as a conduct indicating indifference to

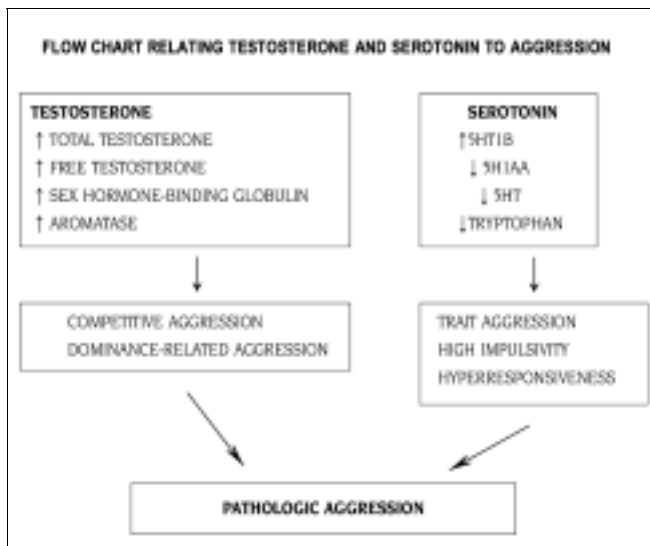
another's person or property such as criminal behavior, dishonesty or abuse [4]. Individual differences in the temperamental traits of impulsivity are relatively stable throughout life. Impulsivity is defined as actions that cannot be stopped or altered once they are initiated, even if the consequences of the action might be undesirable or unpleasant [5]. These traits are likely to result from interactions of biological and environmental factors. Brain structural abnormalities that are caused by genetic, nutritional-environmental factors may produce neuropsychologic dysfunctions. Neurotransmitters, hormones, cytokines, enzymes, growth factors, and signaling molecules are all involved in this complex neurocircuitry that leads towards pathologic aggression. A neural circuit composed of several regions of the prefrontal cortex, amygdala, hippocampus, medial preoptic area, hypothalamus, anterior cingulate gyrus, insular cortex, ventral striatum and other interconnected structures has been implicated in emotion regulation. Functional or structural abnormalities in one or more of these regions or in the interconnections among them can increase the susceptibility for impulsive aggression and violence [6].

Abnormalities of 5-hydroxy-tryptophan and noradrenergic functioning have been implicated in aggressive behavior. The role of dopamine in human studies requires further investigation. Most studies suggest that impulsive aggression is related to lower 5-HT levels in the central nervous system. While some studies show that increased levels of norepinephrine correlate with impulsive aggression, others demonstrate an opposite relationship. The role of norepinephrine in impulsive aggressive behavior is still unclear [7]. Among the various factors implicated in aggression in humans and animals, a distinct link between testosterone and serotonin has been hypothesized as a major contributor [8]. In the present study we review recent findings on the effect of serotonin and testosterone on aggressive behavior and the possible link between them [Figure 1].

Testosterone

Testosterone and other neurosteroids lead to sexual differentiation in the CNS. In laboratory animals it is clear that the CNS is

5-HT = 5-hydroxy-tryptophan



inherently female unless exposed to testicular hormones. Manipulation of the hormonal environment during perinatal development permanently alters both the structure and function of the CNS. Exposing females to testicular hormones masculinizes components of the CNS. Prenatal chemical castration or surgical castration of the male allows the development of a more female-like CNS. In mammals, the sexual differentiation of the CNS has a significant role in shaping sexual preference and other reproductive activities. In addition, it influences food intake and body weight, territorial marking and aggressive behavior, learning strategies, and play behavior. Most likely, in humans, other aspects of cognitive function are affected as well [9]. Testosterone appears to mediate its effects during a critical time period before and after birth, when it sensitizes certain neuronal circuits in the brain and guides the organization of the brain into a "male-like" pattern by inducing or preventing neural cell death. It has been suggested that as a result, in adulthood, when steroids stimulate these circuits again, aggressive behavior is elicited through modulation of specific neurotransmitter pathways. However, it must be remembered that hormones themselves do not directly cause behaviors; rather they induce chemical changes in certain neurons, affecting the likelihood of certain behavioral outcomes as a result of modulation of particular neural pathways [10].

Testosterone acts as a prohormone which, when converted into 5-alpha-dihydrotestosterone, acts on androgen receptors, or when converted to estradiol by the enzyme aromatase, acts on estrogen receptors. There is overwhelming evidence that most of the effects of testosterone in mediating aggression occur after aromatization [11]. Furthermore, the intensity of aggressive behavior was directly correlated with the aromatase activity in the posterior hypothalamus [12]. Men, in general, are much more aggressive than women – a fact that has led researchers to investigate possible links between levels of male hormones (particularly testosterone) and aggressive or criminal behavior. Testosterone may affect levels of aggression beginning early in life. In a study conducted among 28 male and 20 female preschoolers, children were videotaped while playing. Levels of aggression in social and play situations were observed and

measurements of salivary testosterone levels evaluated. Results indicated a positive correlation in boys (but not in girls) between testosterone levels and serious aggression in social situations, but no correlation with playful aggression [13]. A study of 4,462 men revealed that the overall picture among the high testosterone men is one of delinquency, substance abuse and a tendency toward excess aggressive behavior. These men have more trouble with people like teachers while they are growing up, have more sexual partners, are more likely to show disciplinary problems during their military service and to have used "hard" drugs, particularly if they had a poor education and low incomes [14]. Measurements of testosterone saliva levels in 692 adult male prisoners showed that inmates who committed violent or sexual crimes had higher testosterone levels than inmates who were incarcerated for property crimes or drug abuse. This study also shows that inmates with higher testosterone levels violated more prison rules, especially those involving overt confrontation [15]. When salivary testosterone levels of young adult delinquents were compared with levels in a group of college students, matched for age, gender and race, the delinquent subjects had higher testosterone levels than the student controls, a finding that was true for both male and female subjects [16].

It can thus be concluded that high testosterone levels play a role in some criminal behavior, particularly when other risk factors such as low socioeconomic status are present. High testosterone levels have also been found in cases of antisocial behavior in a subtype of alcoholics. Levels of free testosterone, total testosterone, and sex hormone-binding globulin (which influences total testosterone concentration) were measured in 61 men undergoing forensic psychiatric examination. All subjects had been detoxified from drugs and alcohol while hospitalized or in prison. High concentrations of total testosterone and SHBG were related to type II alcoholism (a strongly genetically influenced type of alcoholism seen primarily in males, and associated with earlier onset, a more severe course, and criminality). In addition, total testosterone and SHBG were related to antisocial personality disorder and to socially deviant behavior, as reflected by scores on the Psychopathy Checklist, and free testosterone was strongly associated with the psychopathy-related scales of the Karolinska Scales of Personality [17].

In general, women have low testosterone levels. In order to learn more about the effects of this "male" hormone in females, saliva testosterone levels in 87 female inmates in a maximum security prison were compared with the violence levels of the crimes the subjects had committed, as well as the levels of aggressive dominant behavior they exhibited in prison. A direct link between testosterone and aggressively dominant behavior in prison was found. Further analysis indicated that increasing age is linked to reduced criminal violence and aggressive dominance in female prisoners, both directly and indirectly through lower levels of testosterone that come with age. Five women with the lowest testosterone levels were described by prison staff members to be "sneaky" and "treacherous." Observing the well-established link

SHBG = sex hormone-binding globulin

between testosterone and dominance, it is hypothesized that when dominant high testosterone inmates face confrontation, they act openly and directly, while low testosterone inmates, because they are less dominant, need to be more "sneaky" in dealing with others [18].

The conclusion derived from accumulating evidence in humans and animals indicates that high testosterone levels are related to dominance-related aggression implicated in normal and pathologic behaviors.

Serotonin

The brainstem raphe 5-HT system is the most widely distributed neurotransmitter system in the brain. Serotonergic raphe neurons project diffusely to a variety of brain regions (e.g., cortex, amygdala, and hippocampus). In addition to its role as a neurotransmitter, 5-HT is an important regulator of morphogenetic activities during early brain development as well as during adult neurogenesis and plasticity, including cell proliferation, migration, differentiation and synaptogenesis [19].

In humans, non-human primates and other mammals, preclinical and clinical studies have accumulated an overwhelming body of evidence indicating that 5-HT signaling is a major modulator of emotional behavior, including anxiety and impulsivity as well as aggression, and integrates complex brain functions such as cognition, sensory processing and motor activity [20]. The diversity of these functions is due to the fact that 5-HT orchestrates the activity and interaction of several other transmitter systems. 5-HT may be viewed as a master-control neurotransmitter within a highly complex system of neural communication mediated by at least 14 pre- and postsynaptic receptor subtypes and subunits. 5-HT synthesizing and metabolizing enzymes, and the 5-HT transporter, play an important role in the regulation of 5-HT, which acts as a chemical messenger. 5-HT-mediated behaviors may be diversely expressed and range from minor personality accentuations (characterized by impulsivity, hostility, irritability, psychopathic deviance or violence, or by more clear-cut personality dysfunction such as antisocial, borderline, narcissistic and histrionic personality traits or disorders) to major psychiatric disturbances (suicidal behavior, overt aggressive behavior, intermittent explosive disorder, pathologic gambling, pyromania, bulimia, and some types of substance or alcohol abuse) [21]. One of the most replicated findings in psychobiology is the observation of lower 5-hydroxyindolacetic acid in the brain and cerebrospinal fluid of subjects with impulsive aggression and suicidal behavior. Low or lower than average 5-HIAA concentrations in cerebrospinal fluid have been reported in individuals who display inappropriate aggression as children, engage in frequent impulsive and violent criminal behavior, exhibit excessive alcohol abuse and dependence, and in high lethality suicide attempters as opposed to low lethality suicide attempters. Lifetime levels of aggression were found to be higher among individuals with lower CSF levels of 5-HIAA suffering from depression. In contrast, the dopamine and norepinephrine systems

do not appear to be as significantly involved in suicidal acts, aggression, or depression. [22].

In a study of wild and captive primates, 49 male rhesus monkeys were studied for 4 years. During this time, young monkeys were undergoing a very dangerous period of life during which they migrated from their own groups to new social groups. Between 30% and 50% of the monkeys died during this period, often from violent encounters with other monkeys. (This particular colony of monkeys has no natural enemies.) At the beginning of the study, 5-HIAA levels were measured and the monkeys were divided into four groups: low, mid-low, mid-high, and high 5-HIAA. Twenty-seven of the monkeys were observed in the wild and the monkeys' aggressive acts were recorded. The aggressive acts of all 49 monkeys while in captivity, as well as the monkeys' fight-related scars and wounds, were also recorded. Low CSF 5-HIAA concentrations were predictive of the early death of 11 subjects of the monkey group that were either known or presumed dead. Direct observations of aggressive behavior showed that subjects that died had engaged in high rates of escalated aggression and exhibited a trend to engage in more overall aggression. Of the six dead monkeys whose bodies were recovered, all four who died violently had low 5-HIAA levels, while the two monkeys that died of illnesses had 5-HIAA levels similar to those of the surviving monkeys. While monkeys with low 5-HIAA levels were more violent than the high 5-HIAA monkeys, they also had other dangerous personality traits. They migrated at earlier ages when they were less prepared to defend themselves, were more likely to take life-threatening risks such as spontaneous jumping at dangerous heights when moving from tree to tree, and were most likely to be caught repeatedly in traps. [23]. The increased death rate among monkeys with low 5-HIAA levels is consistent with the results of a 1993 study conducted in a mixed-diagnosis group of 73 male psychiatric patients examined between 1976 and 1990 and diagnosed as suffering predominantly from schizophrenia and depression. Seven of these patients later died before the age of 40. All seven had markedly lower CSF 5-HIAA levels than the surviving patients, and six of the seven died either in homicides, suicides, or "suspicious" accidents [24].

An increase in plasma prolactin when the drug fenfluramine is administered is one measure of the responsiveness of the serotonergic system. The administration of the serotonin-releasing agent D-fenfluramine to 35 healthy subjects (20 females and 15 males) caused an inverse correlation between measures of serotonin function and measures of hostility and aggression in male subjects [25]. These data provide modest support for the theory of a link between reduced serotonergic activity and increased trait aggression in healthy males. No similar correlation was seen in female subjects. A fenfluramine challenge to 97 personality-disordered patients revealed that those with a history of self-injury or suicide attempts displayed evidence of abnormalities of the serotonergic system [26]. Research on deactivation of 5-HT receptors also indicated that 5-HT is connected to impulsivity and aggression-related behavior. The 5-HT_{1B} receptor was the first subtype to have its gene deactivated. These receptors are located predominantly at presynaptic terminals where they can inhibit release of 5-HT. Wild-type and homozygous null mutant (5-HT_{1B})

5-HIAA = 5-hydroxyindolacetic acid
CSF = cerebrospinal fluid

showed more rapid, more intense, and more frequent attacks when being intruded than the non-isolated male wild-type [27]. In contrast to 5-HT1B knockout in mice, 5-HT1A knockouts are less reactive and possibly less aggressive but show more anxiety-related behavior than control mice [28]. In humans, significant sib-pair linkage of antisocial alcoholism was associated with 5-HT1B gene HTR1B G861C polymorphism and the short-tandem repeat locus D6S284 [29].

The first step in 5-HT biosynthesis in 5-HT neurons is catalyzed by the rate-limiting enzyme tryptophan hydroxylase. Involvement of L-tryptophan availability and of TPH activity in impulsivity, aggressiveness, and associated suicidality has been reported in several studies of psychiatric patients or offender populations [30]. An increase was recently observed in aggressive responses on a free-operant laboratory measure of aggression following experimental tryptophan depletion in healthy males, supporting the hypothesis that low plasma tryptophan concentration and associated decrease in brain 5-HT facilitates aggression-related behavior [31].

Although some studies show a controversial trend, i.e., that elevated serotonergic activity leads to increased aggression [32], the majority of research data in humans and animal models do show a correlation between aggressive behavior and low CNS serotonergic activity. This is demonstrated by low CSF 5-HIAA levels, fenfluramine challenge, tryptophan depletion, and mice knockout paradigms.

The relation between testosterone and serotonin

A study that measured CSF testosterone and 5-HIAA showed that:

- CSF free testosterone concentrations were positively correlated with overall aggressiveness, but not with measures of impulsivity.
- CSF 5-HIAA concentrations were negatively correlated with impulsive behavior and with severe, unrestrained aggression, but not with overall rates of aggression. High rates of impulsive behavior were positively correlated with severe, unrestrained aggression, but not overall rates of aggression.
- Dimensional analyses showed that while subjects with low CSF 5-HIAA exhibited high rates of aggression, high CSF testosterone further augmented rates and intensity of aggression in subjects with low CSF 5-HIAA [33].

It is thus concluded that high CSF free testosterone concentrations are associated with competitive aggression, while low CSF 5-HIAA concentrations are associated with severe aggression, which results from impaired impulse control and perseverance [34].

The relationship between impulsivity, aggression, 5-HT function and testosterone in male offenders with personality disorders was investigated in 60 male offenders with personality disorders and 27 healthy controls, using the Special Hospital Assessment of Personality and Socialization score. Non-psychopaths and those with schizoid personality disorders according to SHAPS had enhanced 5-HT function (prolactin response to d-fenfluramine).

Reduced 5-HT function was found in offenders with borderline personality disorders and those with a history of repeated self-harm or alcohol misuse. The 5-HT function was inversely correlated more strongly with impulsivity than with aggression. Plasma testosterone correlated positively with aggressive acts. The SHAPS primary psychopaths had lower initial cortisol and higher testosterone concentrations than controls [8]. Acute administration of testosterone in male rats caused a significant increase in the content of 5-HT2A receptor mRNA and serotonin transporter mRNA in the dorsal raphe nucleus and the density of 5-HT2A receptor and serotonin binding sites in higher centers of the brain. The lack of effect of 5-alpha-dihydrotestosterone, a potent androgen that cannot be converted to estrogen, suggests that the action of testosterone depends upon its conversion to estrogen by aromatase. This may also explain why estrogen, but not testosterone, increased the density of 5-HT2AR binding sites in the caudate-putamen, a brain region where aromatase is scarce.

These findings provide a potential topochemical handle with which to investigate testosterone/estrogen regulation of serotonin-related gene expression. The possible role of interactions between sex steroids and serotonin mechanisms might serve as an etiologic model to psychopathology leading to aggression [35]. The administration of paroxetine, a selective serotonin reuptake inhibitor, did not have any effect on night-time testosterone profiles in healthy male volunteers [36]. In a study examining the relationship between 5-HT, testosterone and alcoholism in the etiology of domestic violence, it was shown that:

- Healthy controls and domestic violence in the non-alcoholic group differed in 5-HIAA concentrations and physical violence scores.
- Healthy controls and domestic violence alcoholic groups differed in testosterone concentrations, alcohol dependence and physical violence scores.
- The domestic violence non-alcoholic and domestic violence alcoholic groups differed in 5-HIAA, testosterone concentrations, physical violence scores and alcohol dependence [37].

Although studies link high levels of testosterone to aggression, this hormone alone does not account for aggressive behavior. In fact, successful athletes and businessmen tend to have high testosterone levels, without being any more violence-prone than their low testosterone counterparts, indicating that testosterone may not act alone in promoting aggression. Rather, aggressive men's behavior may be influenced by high testosterone levels combined with low levels of the brain chemical serotonin. Testosterone is linked more strongly to dominance in general than to aggression. High testosterone levels encourage dominance-seeking behaviors, which put the individual into situations in which frustration of dominance can occur. It is postulated that when a high testosterone man is frustrated in his attempts to achieve dominance, serotonin comes into play, because low serotonin activity is associated with hyper-responsiveness to aversive stimuli and therefore results in a greater likelihood of an intensely negative emotional reaction and, thus, a greater chance of aggressive behavior. It is speculated that the hypothalamus and amygdala, which are prominently associated with both testosterone and

TPH = tryptophan hydroxylase

SHAPS = Special Hospital Assessment of Personality and Socialization

serotonin, play a key role in aggressive responses to situations in which efforts at dominance are frustrated. In comparison to non-aggressive animals, aggressive animals were found to have lower serotonin levels in the hypothalamus and the amygdala. Testosterone action in both of these brain structures was shown to increase aggression in various animal species [38].

Conclusions

Biological influences are not the only pathway leading to individual differences in personality dimensions, behavior, and psychopathology. Complex traits are most likely generated by a complex interaction of environmental and experiential factors with a number of biological factors, among which testosterone and serotonin play a major role. Recent genetic studies on 5-HT receptors, transporters, and modifying enzymes have shown that although these substances have only a modest impact, they affect many developmental processes throughout ontogeny as well as compensatory mechanisms.

The therapeutic application of these findings includes the use of agents that increase 5-HT, either by facilitating its release such as fenfluramine or by blocking its reuptake by the various selective serotonin reuptake inhibitors [39]. Chemical castration by antiandrogenic agents, although inefficient for treating general aggression, is used for the treatment of paraphilic sex offenders [40].

It is becoming increasingly evident that many neurotransmitters and hormones are expressed at early periods of neural development and it is likely that they participate in the structural organization of the nervous system. A major challenge is therefore the identification of specific neural mechanisms that underlie aggressiveness and impulsivity for the purpose of early identification, prevention and the treatment of individuals who are prone to violent acts.

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