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The Role of Serotonin in Aggression and Impulsiveness

Fatih Hilmi Çetin, Yasemin Taş Torun and
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Abstract

Serotonin is a neuromodulator that has a critical role on the regulation of essential events in neuronal and glial development, such as cell proliferation, differentiation, migration, apoptosis, and synaptogenesis, and acts as a developmental signal. It has been known that a serotonergic system is associated with many psychiatric disorders. The serotonergic system also predominates on the etiopathogenesis of two important endophenotypes: impulsivity and aggression. Impulsiveness is defined as personality trait and an implusive temperament is associated with clinical conditions such as pathological gambling, eating disorders, and borderline personality disorder as well as being a risk factor for self-harm, suicide, and emotional liability. Aggression is not a personality trait like impulsivity, but it is the behavior of harm or injury to others. Besides being a natural human behavior toward survival, aggression can be harmful to the individual and the community when it is constant and excessive. In this chapter, we aimed to review the role of the serotonergic system on impulsivity and aggression, which are two important endophenotypes that identified in many psychiatric disorders.

Keywords: serotonin, aggression, impulsivity, impulsive aggression, psychiatric disorders

1. Introduction

Serotonin is a neuromodulator that acts as a developmental signal [1]. The serotonin is formed by decarboxylation of the 5-hydroxy-tripotafan that synthesized from tryptophan via the tryptophan hydroxylase enzyme [1]. Serotonin has a critical role on the regulation of essential events in neuronal and glial development, such as cell proliferation, differentiation, migration, apoptosis, and synaptogenesis [2]. Because of this broad spectrum of serotonin functions, pathologies in serotonergic system have been held to account on many psychiatric

disorders such as mood disorders, anxiety disorders, attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASDs) [3]. Consider of heterogeneous clinic and different symptom clusters of psychiatric disorders, the serotonergic system predominates on the etiopathogenesis of two important endophenotypes: impulsivity and aggression [4, 5]. Impulsiveness is defined as personality trait, which is a multidimensionality [6]. An impulsive temperament is associated with clinical conditions, such as pathological gambling, eating disorders, and borderline personality disorder as well as being a risk factor for self-harm, suicide, and emotional liability [3, 7]. Brain imaging and pharmacogenetic studies have demonstrated that serotonin dysfunction is associated with impulsive behaviors [8]. Aggression is not a personality trait like impulsivity, but it is the behavior of harm or injury to others [9]. It is harmful to the individual and the community when it is constant and excessive, besides being a natural human behavior toward survival [9]. Three types of aggression have been defined as psychotic, impulsive, and proactive [4]. The serotonergic system is associated with impulsive aggression which is manifested by provocation rather than proactive aggression which is goal-oriented and planned [4]. Nowadays, researchers are directed to endophenotypes in psychiatric diseases with heterogeneous clinic in order to develop new treatment methods and to elucidate etiopathogenesis. In this chapter, we aimed to review the role of the serotonergic system on impulsivity and aggression, which are two important endophenotypes that identified in many psychiatric disorders.

2. Impulsivity

Impulsivity is defined as the tendency to exhibit behavior without adequate mental assessment of possible outcomes [10, 11]. From this point of view, it can be said that impulsive dimension can be mentioned in the process of thought up to behavior [12]. In this dimension, there have been different definitions such as impulsive choice, impulsive reflection, and impulsive action that can be measured by different assessment tools that have subjective or objective qualities [10, 13, 14]. Impulsive choice described as prefer less valuable prize in soon afterwards rather than the more valuable prize in the distant future, the inability of the individual to gather adequate data on the risks describes as impulsive reflection and a lack of motor inhibition described as impulsive action [15]. The Iowa gambling test provides data about impulsive choice known as delay-discounting [16]. Stop-signal reaction time and go/no go tasks are objective assessment methods that assess motor inhibition. In these tasks, individuals should wait until the appropriate signal arrives and stop the movement when no go or stop signal is received. "Waiting impulsivity" described as the failure to start the movement and "stopping impulsivity" described as the failure to stop or restrict the movement. The Barratt impulsivity scale and impulsive behavior scale are subjective self-report scales, each with different subscales and provide data on different dimensions of the impulsivity [10, 12, 13, 15, 17–19].

The main pathophysiological mechanism is the disruption of reciprocal equilibrium in corticostriatal cycles [10]. Impulsive behaviors come out as a result of impaired inhibitor function of the prefrontal cortex (PFC) to delay the award and stopping or restricting the behavior,

additionally increased striatal output to achieve a small and certain but definite near future reward rather than the far-future reward, with a high value but a low degree of uncertainty [10, 13, 15].

Recent studies showed that the basic region that rejects the award postponement when the award is quick earning despite small was nucleus accumbens; contrary the basic region that provides inhibition is the orbitofrontal cortex [20, 21]. Anterior cingulate cortex and right inferior frontal gyrus are two other important regions for inhibition [22, 23]. Nucleus accumbens is also associated with impulsive cycle inflicting from the striatum, also accompanied by amygdala and hippocampus [24]. This network includes dopaminergic, noradrenergic, and serotonergic neurotransmission.

Increased impulsiveness is associated with many psychiatric disorders, although healthy individuals have a personality trait and an advantage in situations where the organism needs to move quickly [10]. ADHD, substance abuse, eating disorders, bipolar disorder, behavioral addictions, and borderline/antisocial personality disorders are typical psychopathologies associated with impulsivity [25]. In these disorders, impulsive behavior patterns can be described in many expressions; but aggression is the most accentuated and evidence-based one.

3. Aggression

Aggression is the pattern of behavior that an individual exhibits in such a way as to damage himself or environment [4]. Natively, aggression is necessary to survive. For example, to protect ourselves and our beloved ones from danger, to supply the food and water for survive, and to react to possible risks of the organism on threat [26]. Investigating aggressive behaviors by subcategories is beneficial both in clarifying etiopathogenesis and in adjusting the treatment process. In previous papers, aggression had been categorized as offensive and defensive such as a dangerous or evasive response to a sense of fear, the most frequently preferred classification in the recent literature categorized into three groups: impulsive, proactive (also known as organized, instrumental, or predatory), and psychotic. Impulsive aggression (54%) is the most common category followed by proactive aggression (29%), and psychotic aggression (17%) [27, 28]. As predicted, psychotic aggression is a process related to positive symptoms of psychosis, such as hallucinations or delusional content. In proactive aggression, the individual exhibits this behavior in a planned manner to achieve a blazing benefit such as money or revenge. Impulsive aggression is a behavioral pattern which is accompanied by physical symptoms after stimulation of the sympathetic system, often associated with feelings of fear, inhibition, or anger, which are manifested by stress, threat, or provocation [28].

The main pathophysiological mechanism of impulsive aggression is the altered balance—to the detriment of prefrontal cortex—between the inhibitor stimulants from cortex to subcortex/limbic system and excitator stimulant as strong tendency to realizing behavior from cortex [4]. PFC dysfunction results in inadequate risk assessment and top-down inhibition is reduced [4, 27]. Bottom up outputs that have increased frequency and amplitude especially from the amygdala toward the orbitofrontal cortex contribute to impulsive aggression [27, 29]. In many human and

animal studies, ventral PFC has been shown to be associated with impulse and aggression [30]. Antisocial behaviors are also observed in specific lesions of ventral PFC [30, 31].

4. Serotonin on impulsivity

A significant part of serotonergic innervation in brain structures is derived from the dorsal raphe nucleus (DRN) [32]. It has been shown to increase premature response in the lesion of serotonergic areas at DRN by 5-choice serial reaction time task (5CSRT) although increased correct response [33]. These findings point to the role of serotonergic regulation in organizing behavior to optimize the performance of the cortex [34]. What a serotonin-stimulated neuron will ultimately do is related to the balance between the serotonergic receptors on it [35]. In addition, there are nonserotonergic neurons in the projection fields of raphe nucleus in PFC, where 5HT1A and 5HT2A receptors are postsynaptic located [36]. In PFC, 80% of the glutamatergic neurons and 25% of the GABAergic neurons have 5HT1A and 5HT2A receptors distributed in Ref. [36]. The 5HT2A receptor activates the neuron and increase glutamate release by the contrast with 5HT1A receptor that decreases glutamate release [34]. In molecular genetic studies, 5HT2A is the most prominent receptor in the role of serotonin on impulsivity.

5HTR2A is located in the genomic chromosome 13q14-q21 and contains three exons [37]. This gene codes for a receptor associated with the G protein, and this receptor stimulates phospholipase C, which reduces protein kinase C activity [37]. 5HT2A is most commonly expressed in the hippocampus, amygdala, and nucleus accumbens [38]. The 5HT2A receptor is associated with many common psychiatric disorders such as major depression, obsessive-compulsive disorder, anorexia nervosa, and schizophrenia. Dopamine and 5HT have also been shown to play an important role in the regulation of attention and response control in frontal cortex by animal models [39]. In the psychopathology mentioned above, impulsivity is one of the three core symptom clusters of the disease, ADHD is especially prominent at research. Therefore, in this section, ADHD/impulsivity will be discussed in the context of serotonin. Continuation of sedative effects of methylphenidate in knockout mice inhibited dopaminergic gene function supports the role of other systems. In this model, hyperactivity was also observed to be suppressed with fluoxetine. This effect is thought to be mediated by an increase in the concentration of extracellular serotonin through blockade of the serotonin transporter. In the direction of these findings, it has been suggested that the effect of methylphenidate on impulsivity also be demonstrated by increasing serotonin levels [40, 41]. The data obtained from pharmacological studies, which showed that stimulated striatal 5HT2A receptors increase dopamine release and regulate hyperactivity, confirm that the serotonergic and dopaminergic requirements are in interaction to mediate hyperactivity behavior [42]. Serotonin may affect ADHD and other impulsive behaviors indirectly by regulating dopaminergic functions. The nature of this regulatory effect is complex. It has been demonstrated that serotonergic neurons have inhibitory effects on dopaminergic neuron bodies in the midbrain region; both excitatory and inhibitory effects on dopamine projections in striatum, nucleus accumbens, and prefrontal

cortex by animal models [43, 44]. When serotonergic agonists supplied to striatum, it has been leading to inhibited striatal neuronal firing, decreased in synaptic dopamine, which may result in reduced synthesis or release of dopamine in neuronal projections. That effect has been thought to be mediated by the serotonergic receptor 5HT2A. By way of these data, it has been thought that 5HT2A receptors may contribute to the development of ADHD [45]. Interest in the 5HT2A receptor in ADHD began with the observation that decreased hyperactivity in mice given selective 5HT2A antagonists [42]. It has been shown that the 5HT neurotransmitter system, in parallel with the typical course of ADHD, develops an age-related developmental pattern, for example in developmental studies in monkeys, the 5HT receptor binding increased during infancy and childhood, peaked before puberty and slowly decreased during adolescence and early adulthood [46]. In humans, the 5HT2 receptor binding at 6 years was found to be higher than in neonates and 13–14 years of age [47]. The main result of activation of the 5HT2A receptor by serotonin is reduced noradrenalin and dopamine levels and increased glutamate levels [35]. In this context, 5HT2A antagonism contributes to attention functions by causing an increase in dopamine noradrenalin levels. In the light of those information, it has been aim to clarify the subtypes of impulsivity by referring to some important studies that have recently been made. The 5CSRT is a test for assessing impulsivity, as well as providing information on attention functions used in animal studies [48]. In that task, the individuals learn to get food by pressing the button after a certain goal. The pushing of the button by the animal without showing the target is regarded as a premature response and displays the waiting impulsivity [48]. In a study conducted by Fletcher et al., it was observed that 5HT2C and 5HT2A antagonists given to mice have different effects on 5CSRT [49]. While 5HT2A antagonists reduced prematurity responding, 5HT2C antagonists increased. As a result of that the researchers have also indicated that the impulsivity is not only related to the level of 5-HT, but it is also related to the balance between different serotonergic receptors [49]. In a study in which the effect of 5HT2A receptor gene polymorphism [1438G/A] on impulsivity was assessed by go/no go test, individuals with polymorphism were found to have significantly more commission errors [50]. It has been found that 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), a potent 5HT1A agonist, was ineffective on 5CSRT parameters by systemic administration; however, presynaptic 5HT1A autoreceptors at DRN had a markable effect on those parameters [34]. In a study conducted on women with bulimia nervosa in which impulsive behavior patterns were observed, it was determined that there was a decrease in 5HT2A binding in ventral PFC [51].

The decrease in central serotonergic activity was associated with negative emotional state, poor impulse control, aggressive behavior, increased alcohol and nicotine use, and increased food consumption [52]. The tryptophan depletion method reduces the amount of serotonin throughout the brain. In a study conducted with this method, the relationship between impulse serotonin in humans was examined and an increase in premature response was detected. By this means, it has been concluded that central serotonin levels are related to waiting impulsivity rather than stopping impulsivity. Interestingly, it has been determine that tryptophan-depleted individuals had an increase in motivation and accuracy in compliance with individuals who do not have this depletion [53, 54].

5. Serotonin on aggression

Serotonin is the main neurotransmitter in both top-down and bottom-up processes of neurobiological cycles associated with aggression [4]. Serotonergic hypofunction has been found to be associated with impulsive aggression in aggression subtypes [5]. It has been known that polymorphism of metabolic enzymes, carrier proteins, and receptors on the serotonergic system is associated with an increased aggressive behavior pattern [55]. The essential role of serotonin in the etiopathogenesis of impulsive aggression has been determined by brain imaging studies showing an increase in 5HT2A receptor concentration in orbital PFC in aggressive individuals, tryptophan depletion studies, molecular genetic studies that showed individuals who have monoamine oxidase a gene polymorphisms and have early stressful life events lean to aggression and violence at early adulthood period [38, 56–59].

Selective serotonin reuptake inhibitors (SSRIs) are generally recommended in the treatment of impulsive aggression. However, it should be kept in mind that special approaches are needed in special patient groups. For example, SSRIs have been found to be effective in the treatment of aggression in dementia patients and ineffective in patients with traumatic brain injury [27]. SSRIs are generally recommended in the treatment of impulsive aggression [27].

6. Conclusion

In this chapter, it has been argued the relationship between serotonin, one of the basic neurotransmitters, with the two endophenotypes—impulsivity and aggression—in the face of many psychiatric disorder. There is a consensus in the literature that the problems of the subunits of the serotonergic system result with impulsivity and aggression. Nowadays, researchers have elaborated this information and have identified impulsivity and aggression as subtypes. In the last decade, data from both animal and human studies have been suggested that serotonin has more associated with impulsive aggression than with aggression subtypes, with more "waiting impulsivity" in impulsivity subtypes. More clinical studies are needed on this issue in which genetic and neuroimaging techniques are combined in homogeneous samples that are well defined by subtypes.

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