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Neurochemistry of impulsiveness and aggression

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Summary

Aggression is the most frequent social reaction among animals and men, and plays an important role in survival of the fittest. The change of social conditions in the course of development of human civilization rendered some forms of aggression counteradaptive, but the neurobiological mechanism of expression of aggression have not fundamentally changed in the last stages of human evolution. The two different kinds of aggression: emotional, serving mainly as a threat, and rational, predatory, serving for the attainment of goal in the most effective way, have different anatomical and neurobiological background and reciprocally inhibit each other. Aggression is modulated by several neurotransmitter and hormonal systems, of which key role is seemingly played by testosterone, a hormone involved in domination behavior, and serotonin, whose deficit results in increased impulsiveness.

Key words: aggression, testosterone, serotonin, impulsiveness

Evolution is driven by the struggle for existence, so it is not surprising that the aggressive behavior are the most common social reactions among people and animals. Aggression is a very broad notion comprising different types of behavior, which are generally characterized by the fact that they are intentional and intended to harm to the object of aggression, although it does not have to be its main goal, but only a means to achieve other purposes (such as killing animals for food). Human aggression, aggressive anti-social behavior, is a complex phenomenon. DSM-4 defines it as behavior that "is indicated by indifference to another person or property, such as criminal behavior, dishonesty or abuse". [1] Forms of interpersonal aggression, that we will be particularly interested in here, and which can be after Moyer [2] defined as "overt behavior with the intent to cause damage or other unpleasantness to another person'', are very diverse, ranging from verbal images, and ending with full physical violence which has been defined as the use of physical force to violate the integrity, cause personal injury, or enforce a specific behavior.

These extreme forms of aggression are common in individuals characterized by impulsivity, the tendency to initiate actions that later cannot be stopped or altered, even if their effects can be undesirable or unpleasant [3]. A certain level of aggressiveness is beneficial in the fight for survival, hence the aggressive behaviors are rewarded and

give pleasure to the aggressor. With the development of human societies, aggression has lost much of its adaptive importance and became a destructive factor, but changes in the brain do not keep up with the civilization development, especially in the limbic system, responsible, inter alia, for aggressive behavior. Recently, more and more often we hear of the senseless acts of impulsive violence on a massive scale, taking the form of massacres of defenseless victims, to mention just about Anders Breivik on a picnic on the island of Utoya, James Holmes in the cinema in Denver and Adam Lanza at school in Newtown. From the perspective of history, we must say that now is not so bad – while the XIII-XVIII century in Europe was often a period of mass executions by faggoting and impalement, and the XIX century was an age of public executions, decimation of the rebels, easy ladling of major penalty and routine torture, today in most countries (after the 8th amendment of the U.S. Constitution) the prohibition of torture or cruel punishment was introduced, and less and less frequently the law allows the death penalty and corporal punishment (even in schools).

It seems to me that the dramatic symptoms of aggressiveness occurring in the contemporary, rather less violent society, are connected with another type of hostile social interaction characteristic of the man – hate. There are at least two types of hate – irrational hatred, drawn from a deep anthropological instinct, example of which may be racial or religious hatred, and hatred associated with experienced harm and injustice, thus having some rational basis [4]. This hatred we see in the ever-rising tide of violent behavior, expressed not so much in physical violence, as in verbal aggression, insults and calumnies. Aggressive and hateful behaviors are usually overt (demonstrations, parliamentary debates), but now thanks to the Internet are often anonymous and gain expression. It is no wonder that the neurobiology of aggressive, impulsive and hateful behavior rises a growing concern, especially as such behaviors become socially destructive.

Putting aside for another occasion the fascinating but difficult problems of neurobiology of hatred, we will be here dealing with aggressiveness and impulsiveness, that does not need to be culturally conditioned and occur throughout the animal kingdom, and thus can be studied in a controlled experiment. They have a distinct neurobiological substrate and may result from the interaction of biological and environmental factors. Structural brain abnormalities resulting from genetic and environmental - nutritional factors, can cause functional problems in the circuits regulating emotions. The circuit associated with aggressiveness is extensive and includes structures of the prefrontal cortex, amygdala nuclei, hippocampus, medial field of preoptic area, hypothalamus, anterior cingili gyrus, insular cortex, ventral striatum, and many other interconnected areas. Neurons in this circuit transmit information between them by means of a neurotransmitters and other signaling molecules. Functional or structural abnormalities in one or more of these structures, or the connections between them, may increase the susceptibility to excessive stimulation, leading to pathological and impulsive aggression and violence [5]. Thanks to research by Alan Siegel [6] we know about the major structures governing two fundamentally different types of aggressiveness: predatory and emotional. Predatory aggression, rational, of hunting type, can be invoked by teasing of lateral fornix hypothalamus, the ventral part of the periaqueductal gray matter (PAG)

and tegmentum mesencephali area containing neurons that produce dopamine ventral. Aggressive reaction caused by the teasing – predatory attack – requires planning and strategy and must therefore involve the cerebral cortex [7].

Emotional aggressiveness (in cat occurring as a defensive rage) is controlled by the medial hypothalamus and the dorsal aspect of the PAG. Glutamatergic neurons involved in this behavior are located at the front of the medial hypothalamus and send projections to the dorsal PAG directly, stimulating NMDA receptors there. The neurons in PAG give projections to the somatosensory and autonomous areas of the lower brain stem, the solitary nucleus. In this way, such aspects of emotional aggression are regulated as vocalization and autonomic responses (e.g., pallor or piloerection) [8].

Neuroimaging of brains of aggressive individuals, antisocial ones, indicate the occurrence of these subtle changes in gray matter volume and white matter of the prefrontal and temporal cortex as well as in the putamen. [9] These changes are probably the result of neurodevelopmental disorders [10], thus are innate.

Our knowledge of the importance of the limbic system and hypothalamus in human aggression is based on studies of correlation of behavior (and the occurrence of aggressiveness) in patients with neurological disorders. Aggression is common in cases of temporal lobe epilepsy, temporal lobe sclerosis, tumors in this area and in other areas of the limbic system and hypothalamus. These data together with the results of experiments on animals show that indeed the limbic system modulates the hypothalamus and PAG functions, and thus damage to the limbic structures significantly interfere with regulatory mechanisms that modulate aggressive behavior, leading to loss of control over this type of behaviors [5].

From a practical point of view, more interesting are neurochemical correlates of impulsivity, aggression and hatred because in contrast to the anatomical changes, they can be modified with chemical substances – drugs. In the signal transmission in the aforementioned complex cortico-limbic-hypothalamic neural circuit, which stimulation leads to the pathological aggression, many neurotransmitters, hormones, cytokines, enzymes, and neutrophins are involved [11].

In examining the role of signal substances in the aggressiveness and impulsiveness much attention is given to the male sex hormone (produced also in the body of females) – testosterone, and neurotransmitter acting as the central trophotropic state factor – serotonin.

Testosterone

Studies of potential links between the level of male hormones (especially testosterone) and aggressive and criminal behaviors were undertaken because men tend to be much more aggressive than women. Thus, testosterone has long been seen as the "hormone of aggression", but it must be remembered that hormones directly themselves do not result in a specific type of behavior, but rather cause chemical changes in specific neurons, changing the likelihood of certain behaviors as a result of modulation of individual neuronal pathways [12]. Testosterone is not "ultimate hormone", but can be further converted. Under the influence of 5α-reductase, an enzyme found in high

concentrations in the additional male genitals, it is converted to 5α-dihydrotestosterone, which much more strongly than testosterone acts on androgen receptors. However, under the influence of aromatase, an enzyme present in the adipose tissue, brain, skin, and, of course, in the female gonads, is converted to oestradiol, which acts on the estrogen receptors. There is ample evidence that most of the effects of testosterone leading to induce aggression occur after aromatization [13]. Studies on the correlation between aggressive behavior and testosterone levels in the body are facilitated by the fact that testosterone can be measured in saliva, so sampling for testing is stress free, which is especially important in the study of child aggression.

Research on preschool children, consisting of observation while playing and measurement of testosterone in saliva, showed that in boys but not in girls, testosterone levels are correlated with aggression "for real", but not aggression for fun – playful aggression [14]. Studies on a large (more than 4 400) sample of males showed that individuals with high levels of testosterone are prone to crime, substance abuse and extreme aggression. They had more problems with the teachers at school, more disciplinary problems during military service, and have used more hard drugs, especially when they were coming from the economic and educational lowlands, but they also had more sexual partners [15]. The latter indicates that aggression can promote and strengthen reproductive success and be strengthened as a trend in the population. Many studies have been conducted among criminals, especially when it turned out that testosterone levels are higher in prisoners than in students [16]. As might be expected, prisoners with high levels of testosterone often violated prison rules, especially in cases of overt confrontation [17], and those who have committed violent or sexual offenses had higher testosterone levels than prisoners convicted for crimes against property or possession of prohibited substances [15].

The entire research suggest that high levels of testosterone is associated with antisocial and criminal behaviors as well as with type II alcoholism, social, deviant behavior and level of psychopathy measured by the Karolinska Scales of Personality 18].

Although testosterone is the male thing, and plasma testosterone levels in the women are about ten times lower (3.34 to the 8.48 ng/ml for male students, 0.33 to 1.22 ng/ml for female students) [19], this hormone also affects aggression in women. A study of 87 imprisoned women as particularly dangerous convicts, based on determining correlation and the level of testosterone with violence acts performed by them and the level of aggressive dominant behavior in prison showed – as expected – a strong correlation between the level of testosterone and aggressive behavior, and in addition violence and domination was decreasing with age, which may be associated with lower testosterone levels. Five women with the lowest levels of testosterone have been described by prison staff as "sneaky" and "perfidious". It can be assumed that when the dominant female prisoners with high levels of testosterone act openly during confrontation, then the less dominant, with lower levels of this hormone, in dealing with others to achieve their goals do not use overt aggression, but act "deceitfully" [20].

Concluding, it seems that high level of testosterone is associated with dominance aggression, involved in normal and pathological behaviors, namely aggression thought over, of predatory type.

Serotonin

Second, in addition to testosterone, extremely important signal substance for impulsivity and aggression, is serotonin. The role of the serotonin system and its interaction with testosterone discuss in detail Birger et al [11].

Serotonin system, coming out of brainstem raphe nuclei, serves as the trophotropic state system [21], which regulates the activity of the entire brain towards promoting activities directed to the inside, in order to maintain balance, renew energy resources, rest, sleep and mood. It is the most widespread system in the brain. Serotonergic raphe neurons are very rich in terminals (up to 5 million per neuron) and send projections to various brain regions (e.g., cortex, amygdala and hippocampus) contacting with nearly all the neurons in the brain, while there where there are not formed classical synaptic connections, so called volume transmission takes place. In addition to its role as a neurotransmitter, serotonin is an important regulator of morphogenetic activity during early development of the brain, as well as during neurogenesis in adulthood and plasticity, thus the proliferation, migration, differentiation of neurons and synaptogenesis [22].

A great deal of research on animals and humans indicate that the serotonin signaling is a major modulator of emotional behavior, including anxiety, aggression, impulsivity, and integrates the complex brain functions, such as cognitive and motor activity and sensory processing [23]. The diversity of these functions is due to the fact that the 5-HT orchestrates the activity and interaction of many other transmitting systems. Serotonin can thus be considered as overriding control neurotransmitter of the entire, a very complex system of neural communication. In the regulation of the activity take part at least 14 subtypes of pre- and postsynaptic serotonin receptors, enzymes synthesizing and metabolizing serotonin and serotonin transporter.

Behaviors regulated by serotonin and related to its deficits may be expressed in different ways, ranging from minor exacerbations of certain personality traits such as impulsivity, hostility, irritability, psychopathic deviance and the use of violence by the more explicit personality disorders such as antisocial traits, borderline personality, narcissism and histrionic disorders, to the great psychiatric disorders (suicidal behavior, open aggression, paroxysmal explosive behaviors, pathological gambling, bulimia, pyromania and certain types of substance abuse, including alcoholism) [24].

In contrast to the testosterone, determination of serotonin levels in the brain is difficult, and its blood levels do not say much about the concentration in the brain. Most of the studies were performed by determining the concentration of the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid, which is a complicated procedure, but which allows to draw conclusions about the activity of serotonin in the brain [25, 26].

One of the most repetitive findings in psychobiology is the finding of reduction in the level of 5-HIAA in the brain and cerebrospinal fluid in subjects impulsively aggressive and with suicidal behavior. Low levels of 5-HIAA in the cerebrospinal fluid have been reported in people who were very aggressive in childhood engaging in criminal and violent impulsive behavior, excessively using or addicted to alcohol, engaged in

serious, life-threatening suicide attacks (as opposed to the attacks not ending fatally that probably in many cases, were coldly calculated and made not to be deprived of life, but to achieve the intended purpose). The level of aggressiveness in patients with depression was higher in patients with low levels of 5-HIAA in the CSF. Unlike the serotonergic system the other two major monoaminergic systems – dopaminergic and noradrenergic – do not seem to be overly involved in aggression [27].

The role of serotonin in aggressiveness and impulsivity was confirmed by the continued for many years research on the rhesus bred in natural conditions. Young males characterized by low level of 5-HIAA in the period of leaving parent colonies were killed more often than young with normal levels of 5-HIAA and their death occurred primarily as a result of fighting. Monkeys with low levels of 5-HIAA were more brutal, but also had other dangerous personality traits: migrated earlier when they were not yet fully prepared to defend, were more prone to undertake risky, life-threatening actions, such as spontaneous jumps on dangerous heights during moving from tree to tree, and often falling into the trap [28].

The role of serotonin in aggressive behavior showed a study on the behavior of mice deprived of 5-HT1B receptors. These receptors are found predominantly in the presynaptic terminals and inhibit the release of serotonin from them. Mice genetically modified – so that did not generated 5-HT1B receptors, thus having a higher level of serotonin in the synaptic cleft – were less aggressive and more anxious [29, 30]. Studies on human siblings have demonstrated relationship of antisocial alcoholism with polymorphism of gene encoding the receptor 5-HTR1B G861C and locus repetitive tandem D6\S284 [31].

Serotonin is formed from tryptophan. Reduction of the tryptophan supply causes rapid decrease in the level of serotonin in the brain. This phenomenon began to be used to study the influence of serotonin on aggression and impulsivity, especially when Delgado et al [32] developed a formula of amino acid drink, which causes rapid reduction in the level of tryptophan in the blood, and Williams et al [33] showed that this drink reduces the concentration of metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid, which proves a reduction in the brain of serotonin content. Using this method, Moeller and al. [34] showed that even 5 h after drinking the potion the level of tryptophan in the blood decreased, and the aggressiveness of the volunteers respondents in the so called "Point Subtraction Aggression Paradigm Test" strongly increased. The first research carried out on men, were then repeated by Marsh et al on women with the same result [35]. After the addition of tryptophan, aggressiveness decreased to the initial level. Within interesting consequences of the application of a cocktail lowering tryptophan should be mentioned the increase in impulsive reaction to injustice. This is tested in the game, "Ultimatum" in which one partner receives a sum of money to be shared with the other partner, but he determines himself how much money give to the partner. Proposals shall be considered fair if he proposes 45%, unfair – if 30%, fraudulent – if 20%. If the partner rejects the proposal, the both lose because the money forfeited

Providing a mixture lowering serotonin levels increased the number of rejections – impulsive reaction to injustice prevailed over rational consent to small but always

a profit [36]. On the other hand, increasing the concentration of serotonin in the synapse by the use of citalopram results in increased acceptance of the unfair proposal, and at the same time results in an increase of reaction condemning infliction harm to others [37].

It should be added that despite the popularity of non-tryptophan cocktail in some studies its application did not result in a substantial increase in aggressiveness [38]. However, about the role serotonin as a factor inhibiting aggression, we also know from other studies, such as with the use of drugs changing its level, like just from that mentioned experiment with citalopram. Also, another serotonin reuptake inhibitor, fluoxetine, decreased impulsive aggression in patients with personality disorders [39]. Similarly in criminals with personality disorders aggressiveness reduced fenfluramine, a drug releasing serotonin from nerve terminals which, however, due to the toxic effects has been withdrawn from the market in 1997.

Evidence for the role of serotonin in aggression also have been found in several studies correlating the level of brain serotonin (or 5-HIAA in the CSF) with aggressiveness. Already 35 years ago Asberg et al [40] showed that low levels of 5-HIAA in the CSF may be a marker of suicide risk and studies form the group of Dådermana and Lidberga group have shown that the poor ability to control impulsivity occurs in people with low levels of serotonin in platelets blood [41] and 5-HIAA in the CSF [42], and such low level may be an indicator of recidivism in the case of crimes of violence [43]. Similar results brought a lot of studies in humans [8], and analogous results were obtained, as mentioned earlier, in monkeys [28].

It is worth mentioning that the well-known aggressiveness occurring after consuming alcohol also has a serotonin component. About half a liter of beer, namely a dose of alcohol that causes its appearance in the blood at concentrations of 0.75-0.78 ‰ (i.e. just below the acceptable limit for drivers in the U.S. and the UK), dramatically reduces the level of tryptophan in the blood after 2 h of consumption [44], so presumably also in the brain [33]. This may explain the increased aggressiveness that occurs in many people after consuming alcohol. Increased aggressiveness was observed after co-administration of alcohol and tryptophan-lowering diet and it can be assumed that the intensification of aggressiveness by the alcohol may be largely related to the mechanism of serotonin [45].

The mechanism of inhibition of aggression by serotonin and its intensification with reducing its level is still being discussed, it is believed that a reduction in serotonin levels causes damage to the inhibitory function and interferes with the processing of motivational stimulus properties [38].

Of course, an interesting issue is the relationship between testosterone and serotonin. Studies in which levels of testosterone and 5-HIAA in the CSF were measured have shown that high levels of free testosterone in the CSF are related to competitive aggression, while low levels of 5-HIAA in the CSF are associated with severe aggression which causes impulse control disorders and perseveration [46]. Also, in the study of criminals, men with personality disorders, a reduction in activity of serotonergic system (in the test with d-fenfluramine) have been shown in offenders with borderline personality and history of repeated self-harm or abuse alcohol. The degree of reduction in serotonin activity correlates more with impulsivity than with aggression, and testosterone levels correlate with aggression [47].

It should also be noted that sex hormones regulate the expression of genes of the serotonergic system, for example by increasing mRNA expression of 5-HT 1A receptor and serotonin transporter in the nuclei raphe, and cause increase of the density of 5-HT2A receptor and serotonin binding sites in the higher centers of the brain. On the interaction between sex hormones and serotonergic mechanisms etiological model of psychopathology leading to aggression can be constructed [48]. There were no reverse dependencies indicated: serotonin reuptake inhibitor, paroxetine, has no effect on the nocturnal profile of testosterone in healthy male volunteers [49].

The study on the relationship between serotonin, testosterone and alcohol in the etiology of domestic violence have shown that low levels of serotonin and high levels of testosterone modulate sensory stimuli used to activate neural pathways involved in fear-induced aggression, and this causes a predisposition to over-reaction to real or imagined risk [50].

Although research associate a high level of testosterone with aggression, this hormone by itself is not responsible for aggressive behavior. In fact, successful athletes and businessmen usually have high levels of testosterone, without being more prone to violence than their counterparts with low testosterone levels, indicating that testosterone cannot act independently to promote aggression. High levels of testosterone are associated with the general tendency to dominate than with a tendency to aggression. Of course, high levels of testosterone can lead to dominant behaviors, which often leads the individual to situations of dominance frustration. It is postulated that when a man with high level of testosterone is frustrated in his attempts to achieve a dominant position, serotonin starts to come into play. The resulting from the situation reduction in serotonin activity is associated with an excessive response to aversive stimuli, and thus greater likelihood of a strong negative emotional response is formed and consequently – an increase chances of occurrence of aggressive behaviors. In comparison to non-aggressive animals, these aggressive ones have lower levels of serotonin in the hypothalamus and amygdala. The activity of testosterone in both brain structures increases during aggression in different animal species [51].

Individual differences in the dimensions of personality, behavior and psychopathology are most often generated by multiple groups of environmental factors and life experience, including a number of biological agents, among which testosterone and serotonin have a prominent place. Recent genetic studies on 5-HT receptors, transporters and enzymes regulating showed that, although these substances have only a moderate effect, they act in many developmental processes during ontogeny and compensating processes.

Possible therapeutic applications of these findings include the use of agents that increase serotonin activity or facilitate the release of serotonin, such as fenfluramine, or by blocking the reuptake of serotonin by various selective serotonin reuptake inhibitors [52]. Chemical castration by giving anti-androgen agents, although not effective in the treatment of aggressiveness in general, is used in the treatment of sex offenders with paraphilia [53].

There is increasing evidence that many neurotransmitters and hormones are expressed in the early phases of development of the nervous system and that they are likely to participate in the organization of structures of the nervous system. The main

challenge of the researchers of aggressiveness is currently to identify specific neural mechanisms that underlie the development of aggressiveness and impulsiveness, and use this knowledge for the early detection, prevention and treatment of people who tend to make acts of violence.

The discovery that biological factors – such as testosterone and serotonin – are essential for the development of predispositions, but do not determine aggressive and impulsive behaviors indicates that even in neurochemically adverse situations psychiatrist has a great chance of effective therapeutic action.

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