Psychology & Neuroscience
ISSN: 1984-3054
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Pontifícia Universidade Católica do Rio de Janeiro
Brasil

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Psychology & Neuroscience, vol. 7, núm. 4, 2014, pp. 601-607
Pontifícia Universidade Católica do Rio de Janeiro
Rio de Janeiro, Brasil

Available in: http://www.redalyc.org/articulo.oa?id=207032913020

PSYCHOLOGY & NEUROSCIENCE

Psychology & Neuroscience, 2014, 7, 4, 601-607
DOI: 10.3922/j.psns.2014.4.20

Aggressive behavior and three neurotransmitters: dopamine, GABA, and serotonin—a review of the last 10 years

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Abstract

Aggressive behavior has received considerable research attention for more than five decades. Although extensively studied, the mechanisms involved in both functional and pathological aggression are still far from elucidated. The regulation of aggression by a wide spectrum of neurotransmitters is well known. Serotonin has shown both inhibitory and stimulating effects on aggressive behavior, depending on the brain region measured and specific receptors where it acts. Dopamine and the mesocorticolimbic system associated with reward seeking behavior are also associated with aggression. Dopamine can sometimes enhance aggression and sometimes reduce the impulsivity that might lead to abnormal aggression. γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter, and its relationship with aggressive behavior is extremely complex and highly associated with serotonin. This review focuses on summarizing the roles played by these three neurotransmitters (serotonin, dopamine, and GABA) in aggressive behavior and analyzing aggressive behavior from both neuropsychology and interdisciplinary perspectives.
Keywords: aggression, dopamine, GABA, humans, mice, prefrontal cortex, raphe nuclei, serotonin.

Received 20 December 2013; received in revised form 03 June 2014; accepted 05 June 2014. Available online 16 December 2014.

Introduction

Aggressive behavior has received considerable research attention for more than five decades (Ferrari, Palanza, Parmigiani, de Almeida, & Miczek, 2005), and the amount of data available on this subject has seen substantial growth in the last 10 years. Aggression is a complex social behavior that evolved within the context of defending or obtaining resources (Nelson & Trainor, 2007) and is a well known part of several mating rituals in a broad variety of species. Animals show aggression to protect themselves and their offspring from predators, in the struggle for females and food, and to maintain a defined hierarchy in the community (Popova, 2008). Traditionally, it has been defined as overt behavior that has the intention of inflicting physical damage on another individual (Soma, Scotti, Newman, Charlier, & Demas, 2008). Two subtypes of aggression have been identified in humans: the controlled-instrumental subtype and the reactive-impulsive subtype. The latter is considered impulsive (usually associated with anger), whereas the former is considered more purposeful and goal-oriented (Nelson & Trainor, 2007). Impulsive aggression is a complex behavioral phenotype, and multiple brain systems contribute to its etiology and high comorbidity with other disorders (Seo, Patrick, & Kennealy, 2008). Instrumental aggression, in contrast, is highly seen in psychopathy (von Borries, Volman, de Brujin, Bulten, Verkes, & Roelofs, 2012) and is indirect aggression in which an individual tries to harm another through the use of social schemes (Vaillancourt & Sunderani, 2011). Aggressiveness *per se* has never been considered abnormal, but many problems can occur when aggressiveness is associated with a psychological disorder (Haller & Kruk, 2006). Aggression, in fact, is a key symptom in a numerous psychiatric disorders such as mood disorders and personality disorders (Veenema & Neumann, 2007). Drug abuse, schizophrenia, autism, and bipolar disorder are just a few examples (Bronsard, Botbol, & Tordjman, 2010; Kloke, Jansen, Heiming, Palme, Lesch, & Sachser, 2011; Soyka, 2011; Voravka, 2013).

Several experiments with animals (Caramaschi, de Boer, de Vries, Koolhaas, 2008a; Kloke et al., 2011; Jansen et al., 2011) have demonstrated the possibility, using proper protocols, to escalate normal aggressive behavior into pathological aggressive behavior.

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Experiencing victory in conflicts against other animals can cause a "winner effect," which can increase aggressive behavior to pathological levels (Kloke et al., 2011). Male rats that attack female, anesthetized, or submissive rats are commonly used as indicators of pathological aggression.

Recently, transgenic mice have been considered a good alternative to the time-consuming and difficult protocol of instigating an escalation of aggression. Targeting specific genes is a promising way to generate animals with much lower thresholds for aggression. However, the differences between the neurobiological mechanisms that govern aggressive behavior in different species are a significant challenge to the development of animal models of escalated aggressive behavior (Miczek, De Boer, & Haller, 2013).

In humans, aggressive behavior has seemed to exponentially increase in the last few decades. According to the World Health Organization, the number of fatal victims in interpersonal conflict in 2002 was almost twice the number of war victims (Krug, 2002). More recent reports showed that at least 700,000 people die each year as victims of aggressive assault (Bartolomeos, Brown, Butchart, Harvey, Meddings, & Sminkey, 2007).

Neurotransmitters are signaling molecules in the nervous system. Their function as signaling molecules depends on receptors that are specific to each neurotransmitter in the synaptic cleft. Examples include serotonin, dopamine, γ-aminobutyric acid (GABA), norepinephrine, and acetylcholine, among many others. These molecules are key factors in a wide range of behaviors. The role of neurotransmitters in aggression is discussed below.

Several neural networks have been associated with aggressive behavior, and studies on aggression have been conducted in many different species including fish (Øverli et al., 2004), lizards (Kabelik, Alix, Burford, & Singh, 2013), song sparrows (Maddison, Anderson, Prior, Taves, & Soma, 2012), cats (Bhatt, Zalcman, Hassanain, & Siegel, 2005), rats, mice, and humans. The hypothalamic-pituitary-gonadal (HPG) axis regulates testosterone levels in the organism (Mehta & Josephs, 2010). High testosterone levels can decrease the activity of the medial region of the orbitofrontal cortex (OFC) within the prefrontal cortex (PFC) and stimulate aggressive behavior (Mehta & Beer, 2009). One of the possible mechanisms by which testosterone can reduce the activity of the OFC is by regulating serotonin. Androgens have been previously shown to downregulate serotonin receptor mRNA expression and serotonin turnover in the medial PFC (mPFC; Ambar & Chiavegatto, 2009). The relationship between the levels of testosterone and cortisol, a product of the hypothalamic-pituitary-adrenal (HPA) axis, known for being physiologically antagonistic to the HPG axis, was found to be associated with the way aggression is expressed (Montoya, Terburg, Bos, & van Honk, 2012). Psychopaths, for example, usually have a higher testosterone/cortisol ratio than normal individuals (Glenn, Raine, Schug, Gao, & Granger, 2011). The relationship between these hormones and the way they regulate aggressive behavior support a dual-hormone hypothesis (Mehta & Josephs, 2010) in which high testosterone/cortisol ratios lead to higher levels of aggression, and low testosterone/cortisol levels lead to evasion of the fight response (Montoya et al., 2012).

The complexity of aggressive behavior, contradictory data on neurotransmitter function under different conditions and in different individuals and brain regions, and various expressions of aggressive behavior in different species and genders reinforce the need for a review of the current knowledge.

Objectives

This systematic review sought to analyze the influence of three neurotransmitters (dopamine, GABA, and serotonin) on aggressive behavior.

Data collection

The data were collected by searching keywords in the scientific databases PubMed (2003-2013) and Web of Knowledge (2003-2013). The keywords were aggressiveness, dopamine, GABA, humans, rats, prefrontal cortex, raphé nuclei, and serotonin. The keywords were combined in groups (up to three words per group). The keyword "aggressiveness" was used in every search to retrieve results related to the subject. The search results were judged by a researcher with experience in the field and then selected or discarded, as described in Figure 1. Of the 198 articles found, 19 were discarded because they were not directly related to the subject. From the remaining 182, 61 were used in this review. The criteria that were used to select the articles that would be used were relevance, year of publication, and distinctiveness. Articles that contained similar information to those in other papers had a lower priority than those with new or seemingly contradictory data.

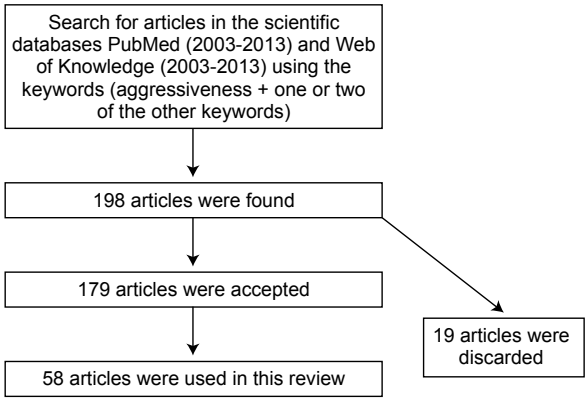

Figure 1. Flowchart of the methodology used in this review.

Serotonin

In the last few decades, the recognition of serotonin (5-hydroxytryptamine [5-HT]) as a key neurotransmitter related to aggressive behavior has grown. Serotonergic neurons originate from raphé nuclei in the brain stem. The axons of serotonergic neurons in raphé nuclei in the midbrain reach almost every structure in the brain (Celada, Puig, & Artigas, 2013). The relationship between serotonin and aggression is extremely complex. Different neural pathways can present different reactions to the same pharmacological manipulation depending on the receptor subtypes that are present in the pathway. There are currently seven known families of 5-HT receptors: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5HT_5, 5-HT_6, and 5-HT_7.

Serotonin and male aggression

Generally, serotonin has an inhibitory action on aggressive behavior (Carrillo, Ricci, Coppersmith, & Melloni, 2009). However, aggressive behavior in its functional form, in which it fulfills a communicative function, is positively related to serotonin levels (Kulikov, Osipova, Naumenko, Terenina, Mormède, & Popova, 2012), whereas pathological forms of aggression are usually inhibited by serotonin (De Boer, Caramaschi, Natarajan, & Koolhaas, 2009). Heightened serotonin activity through the elevation of serotonin precursor levels, serotonin reuptake inhibition, or 5-HT_{1A} receptor agonism is known to reduce aggressive behavior (Nelson & Trainor, 2007). 5-HT_{1B} receptors are mostly located presynaptically on serotonergic neuron terminals in the raphé nuclei to modulate the release of serotonin (Suzuki, Han, & Lucas, 2010). The activation of 5-HT_{1B} receptors inhibits aggressive behavior, independent of serotonin levels. Presumably, the behavioral effects regulated by 5-HT_{1B} receptors reflect the modulation of systems associated with other neurotransmitters (Nelson & Trainor, 2007).

Studies have demonstrated that 5-HT_{1A} receptor agonists potently inhibit aggressive behavior, particularly in animals with high or escalated levels of aggression. Serotonin levels in the PFC in aggressive mice were lower in animals that exhibited higher sensitivity of 5-HT_{1A} autoreceptors (Caramaschi, de Boer, & Koolhaas, 2007). This finding suggests that the inhibition of serotonergic neurons in the raphé nuclei through these autoreceptors may be a marker in individuals with high levels of aggression. Therefore, pharmacological manipulations that target these autoreceptors could be used to lower aggressive behavior. Data that showed that serotonin inhibits aggression eventually led to the "serotonin deficiency hypothesis."

One particularly interesting finding is that serotonin not only regulates the levels of aggressive behavior but also regulates the reaction to aggressive behavior. A study with humans showed that serotonin levels were associated with unfairness in an application of the Ultimatum Game, a well-known protocol that assesses aggressive behavior (Crockett, Clark, Tabibnia, Lieberman, & Robbins, 2008). Whenever the levels of serotonin were lower, the individuals who received an unfair offer were significantly more willing to retaliate, although they reported no mood alteration or changes in judging the fairness of the offer. These data also support the involvement of serotonin in defensive aggression.

In fact, the reduction of defensive aggression levels over generations leads to abnormal serotonin metabolism. The animal model that was used for this experiment was the silver fox. Foxes that were selected for low levels of defensive aggressive behavior expressed much higher serotonin levels in specific brain regions (Popova, 2004). Differences in serotonin levels in the PFC are also considered one of the key factors involved in highly aggressive behavior in some mouse lines, such as the Short-Attack-Latency (SAL) and Long-Attack-Latency (LAL) lines (Caramaschi, de Boer, & Koolhaas, 2008b). These lineages are used as a model in studies of aggression because of their high (SAL) and low (LAL) levels of innate aggression. Veenema and Neumann (2007) reported that SAL mice had a higher level of postsynaptic 5HT_{1A} receptors in the hippocampus and higher binding capacity than LAL mice, accompanied by higher serotonin responsiveness, but no difference was found in presynaptic 5HT_{1A} autoreceptor levels in the raphé nuclei. This is not an isolated case of serotonin stimulating aggressive behavior. Olivier (2004) provided both published and unpublished evidence that 5HT_{1B} receptors can actually induce aggressive behavior instead of inhibiting it. Despite the extensive amount of research on serotonin's relationship with aggression, its precise role is still unclear.

Serotonin and female aggression

Although females are usually not used as models of aggression, maternal postpartum aggressive behavior is one way to induce an escalated state of aggression to generate data on aggressive behavior in females. Da Veiga, Miczek, Lucion, and de Almeida (2011) used a protocol of social instigation in postpartum females to induce aggressive behavior using selective and full agonists of 5HT_{1A} and 5HT_{1B} receptors (8-OH-DPAT and CP-93,129, respectively). 8-OH-DPAT is a well-known and broadly used agonist that potently reduces aggressive behavior, despite being able to induce hypothermia (de Boer & Koolhaas, 2005). CP-93,129 is also used to reduce aggressive behavior and also heightens non-aggressive, non-social exploratory behavior in male mice (de Boer & Koolhaas, 2005) and sniffling and rearing behavior in postpartum female mice (da Veiga, Miczek, Lucion, & de Almeida, 2007). Surprisingly, 8-OH-DPAT, when injected in the dorsal raphé nuclei (DRN), actually increases the levels of aggressive behavior in postpartum females (da Veiga et al., 2011). This finding demonstrates the complexity of the serotonergic system and how it works differently in different genders. Moreover, serotonin levels are related

to the levels of other neurotransmitters, such as GABA, which will be discussed later.

Dopamine

3-Hydroxytryptamine, or dopamine, is a neurotransmitter that belongs to the family of catecholamines (Hansen & Manahan-Vaughan, 2012). The dopaminergic system is involved in movement control, the reward system (Arias-Carrión, Stamelou, Murillo-Rodriguéz, Menéndez-González, & Pöppel, 2010), and the persistence of long-term memory (Rossato, Bevilaqua, Izquierdo, Medina, & Cammarota, 2009). Although dopaminergic neurons represent less than 1% of the total neuron population, they have a profound effect on brain function (Arias-Carrión & Pöppel, 2007). The neural projections of the dopaminergic system include efferents from the ventral tegmental area to the nucleus accumbens and PFC and efferents from the substantia nigra (Arias-Carrión & Pöppel, 2007). There are five different dopamine receptors: D_1, D_2, D_3, D_4, and D_5.

Dopamine's role in aggressive behavior is not yet precisely known. The dopaminergic system is activated when an offensive animal meets a defensive one (Ferrari, van Erp, Tornatzky, & Miczek, 2003). Whenever a resident mouse encountered an aggressive intruder mouse at a regular interval, both dopamine and serotonin levels increased in anticipation of the confrontation. Both neurotransmitters are involved not only in aggressive behavior but also in coping with stress. Both pleasant and stressful events activate the mesocorticolimbic dopamine system (Miczek, Faccidomo, de Almeida, Bannai, Fish, & Debold, 2004). Growing evidence suggests the participation of dopamine in aggressive behavior. The dopamine transporter is responsible for controlling extracellular dopamine levels, and dopamine transporter knockout mice exhibit higher expression levels of D_1 and D_2 receptors, higher aggressiveness, higher extracellular dopamine levels, and lower concentrations of D_1 and D_2 receptors (Rodriguiz, Chu, Caron, & Wetsel, 2004). These are surprising data because D_1 and D_2 receptor antagonists inhibit aggressive behavior (Nelson & Trainor, 2007). One well-known example of such an inhibitory capacity is the D_2 receptor antagonist risperidone, which is commonly used to reduce aggressive behavior associated with arousal and stress (Nelson & Trainor, 2007). The use of risperidone is common in patients with autism and schizophrenia, in which both conditions present with abnormal aggressive behavior (Bronsard et al., 2010; Soyka, Graz, Bottlender, Dirschedl, & Schoech, 2007).

Dopamine's involvement in the regulation of aggressive behavior might be associated with competitive motivation. Aggressive behavior arises when conflict occurs between two individuals, and interpretation of the confrontation as a fight for resources makes dopamine's involvement quite predictable because of its role in the reward system (Arriás-Carrion et al., 2010). Moreover, dopamine levels are also associated with risk-taking, in which risk evaluation is based on the size of the reward that is implied in the risk, making its role in aggression even more important. An experiment performed by Riba, Krämer, Heldmann, Richter, and Münte (2008) highlights this point. Pramipexole is a D_2/D_3 receptor agonist that is reported to be associated with gambling addiction when used to treat Parkinson's disease. Pramipexole was administered in healthy patients during a simple lottery task as part of a placebo-controlled, double-blind study in an attempt to simulate the effects of this dopamine agonist in patients with Parkinson's disease, which is known to present with lower dopamine levels in nigrostriatal pathways. The results showed a significant increase in the number of risky decisions made by the patients, associated with lower activation of dopamine systems when these decisions were followed by gains that exceeded the patient's expectations. This reduction of sensitivity to reward might explain why the patients were always making riskier decision. According to these authors, this blunting of the reward system leads to the pursuit of even higher rewards because the patients do not feel as rewarded as a normal person would. However, patients who were treated with L-3,4-dihydroxyphenylalanine (L-DOPA), a precursor of dopamine, did not show the same pattern. This difference illustrates the heterogeneity of functions performed by different types of dopamine receptors and complexity of the underlying mechanisms of dopamine regulation of the reward system.

γ-Aminobutyric Acid

GABA and male aggression

GABA is well known as the main inhibitory neurotransmitter in the mammalian brain. It is an extremely anciently derived molecule that is also found in plants, fungi, bacteria, cnidarians, and insects. It exerts its inhibitory actions even in organisms with the simplest of nervous systems, hydrozoans (Gou, Wang, & Wang, 2012). It is synthesized from its precursor, L-glutamate, through a process of decarboxylation via the enzyme glutamate decarboxylase (Wassef, Baker, & Kochan, 2003). GABAergic neurons project to virtually all regions of the brain and exert potent regulatory actions on several brain mechanisms. There are three types of GABA receptors: $GABA_A$ and $GABA_C$ are ionotropic, and $GABA_B$ is metabotropic and coupled to a G-protein. $GABA_A$ receptors are the best characterized of the three subtypes (Wassef et al., 2003) and are widely found in the central nervous system, both pre- and postsynaptically (Sankar, 2012).

GABA's involvement in aggressive behavior is mostly associated with its inhibitory action, but some findings have been contradictory. Studies that directly manipulate GABA levels point to an inverse correlation with aggressive behavior (Miczek, Fish, & De Bold, 2003). However, studies that used positive allosteric modulators of GABA, such as alcohol, have reported

enhanced aggressive behavior (de Almeida, Ferrari, Parmigiani, & Miczek, 2005). This increase might be related to the activity of $GABA_A$ receptors in the DRN, as discussed later.

Interestingly, although $GABA_A$ receptor activation is associated with a decrease in aggressive behavior, positive modulators can enhance aggression. $GABA_B$ receptors, in contrast, are directly related to escalated aggressive behavior. Takahashi, Kwa, DeBold, and Miczek (2010a) showed that pharmacological activation of $GABA_B$ receptors in the DRN play an important role in the escalation of aggressive behavior. This finding also sheds light on the interaction between GABA and serotonin because serotonergic neurons in the raphé nuclei are responsible for the regulation of serotonin levels. The many nuances of escalated aggressive behavior are being unveiled, and accumulating data on each isolated neurotransmitter and how neurotransmitters regulate each other will aid the discovery of treatments for pathological aggressive behavior.

GABA and female aggression

$GABA_A$ receptors are associated with offspring protection in females, and their localization in the lateral septum is involved in female aggression (Lee & Gammie, 2009). In this study, benzodiazepines which, like alcohol, are positive allosteric regulators of GABA activity, increased aggressive behavior in postpartum females. Peripheral administration of the $GABA_A$ agonist chlordiazepoxide also enhanced aggression in females, although $GABA_A$ receptors are traditionally associated with the suppression of aggressive behavior. One year later, the same authors (Lee & Gammie, 2010) published a study that investigated the caudal periaqueductal gray and found a different response profile. Chlordiazepoxide did not enhance aggressive behavior, whereas the $GABA_A$ receptor antagonist bicuculline significantly reduced aggressiveness in females but had no effect when injected into the aqueductal gray. Further research is still necessary to elucidate GABA's complex activity in aggressive behavior, but GABA receptors are already a valid therapeutic target for the regulation of aggression.

Neurotransmitter System Integration

As cited above, GABA is well known to regulate serotonin levels because of high receptor expression in the DRN (Takahashi et al., 2010a; Takahashi, Shimamoto, Boyson, De Bold, & Miczek, 2010b). Both $GABA_A$ and $GABA_B$ receptors are involved in the regulation of serotonin levels. The activation of GABAergic receptors on serotonergic neurons can lead to higher serotonin levels in the mPFC and, therefore, can induce aggression. Notably, however, GABA receptors in the medial raphé nuclei (MRN) have no escalating effect on aggressive behavior, showing that serotonin neurons in the MRN and DRN play differential roles in aggressive behavior. This might be attributable to the different areas where these regions project their efferents. The MRN is mostly related to the dorsal hippocampus and medial septal nucleus, whereas the DRN projects to the dorsal striatum, ventral hippocampus, amygdala, nucleus accumbens, and cerebral cortex (Mokler, Dugal, Hoffman, & Morgane, 2009).

The extreme complexity of the activity of these neurotransmitters is one of the major complications in the study of aggressive behavior, and establishing causal relationships between the activities of these neurotransmitters has been difficult. Other neurotransmitters or hormones might also be involved. Higher levels of cortisol, for example, are associated with aggression but only when present in males with high testosterone levels (Montoya et al., 2012). Nitric oxide is associated with lower pain sensitivity, and nitric oxide synthase knockout animals show an increased duration of aggressive behavior (Nelson, Trainor, Chiavegatto, & Demas, 2006). There are many examples of how different neurotransmitters are involved in aggression, but their roles are not precisely known across the many animal models that are utilized to evaluate aggressive behavior. Understanding aggressive behavior in animals is still important because they help us comprehend the evolution of aggressiveness and how individuals of a given species react to predators or competitors before reintroducing them into the wild. The many facets of how the understanding of aggressive behavior can benefit science are usually obfuscated by the "therapeutical use", but that is a misunderstanding of the potential applications for aggression studies.

Perspectives

Several new methodologies can be used to improve our knowledge on how aggressive behavior works. Epigenetics is a rising star, and research in this area has great potential to shed light on how environmental changes regulate and stimulate aggressive behavior. One might investigate, for example, the genes associated with serotonin, dopamine, or GABA receptors or their transporters and how their methylation patterns change when an animal is exposed to aggressive encounters. These changes may be a key factor in explaining enhanced aggressive behavior and discovering new targets that both treat and induce aggression. Challis, Beck, and Berton (2014) optogenetically modulated serotonergic neurons in the DRN to interfere with socioaffective choices after a protocol of social defeat. The specificity of optogenetic methods may be useful to fill some gaps in the current knowledge of serotonergic, dopaminergic, and GABAergic neurons and their interregulation. Aggressive behavior should be viewed not only as a health issue but also from an environmental perspective. The reintegration of animals into their natural environment after trauma or isolation might represent more of a threat to the population. To address this issue, determining how individual differences can change the effectiveness of a given drug can be significantly important. This

kind of analysis would attract substantial interest from conservational institutions and create opportunities for other professionals who are not directly involved in studies of human health, such as ethologists. In the current global conditions of weather, biodiversity, and natural resources, boundaries need to be softened between health research and environmental research, and research on aggressive behavior may provide a major opportunity.

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