Aggressive behavior: A comprehensive review of its neurochemical mechanisms and management

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Abstract
Aggression is a deliberate series of actions that lead to harm, injury, or destruction of another organism, and is the most common factor promoting violent crimes. Beyond being the immediate cause of physical injury, aggressive behavior also produces profound long term emotional disabilities in its victims. When outburst of aggression is comorbid with DSM-IV-defined neuropsychiatric disorders, the offenders are usually given psychiatric care; however, when they appear normal or healthy, their most likely fate is punishment by the law. This punitive approach often increases aggression, thereby promoting the propensity for violent crimes. Antipsychotics are the drugs commonly used for treatment of aggression and violent outbursts. However, the uses of these drugs have serious side effects of catalepsy or impairment of sensorimotor performance. They also affect the defense or flight capabilities of organisms, which further limit their usefulness in aggression. Thus, there is a critical need to search for agents that can selectively reduce aggression without affecting other behaviors or causing any serious unwanted side effects. This review focuses on the types, neurochemical bases, and animal models of aggression, with a comprehensive appraisal of the pharmacological approach to the treatment of the disorder.

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1. Introduction

Aggression is a deliberate series of actions that lead to harm, injury, or destruction of another organism and is the most common factor promoting violent crimes. Beyond being the immediate cause of physical injury, aggressive behavior also produces profound long term emotional disabilities in its victims (Weinshenker & Siegel, 2002). When outburst of aggression is comorbid with DSM-IV-defined neuropsychiatric disorders, the offenders are usually given psychiatric care, but when they appear normal or healthy, their most likely fate is punishment by law (Weinshenker & Siegel, 2002). However, this punitive approach often increases aggression, thereby promoting the propensity for violent crimes.

Although aggression is detrimental to the society, it also serves as a useful defensive purpose for obtaining the desired goal of self-preservation in life-threatening events (Moffitt et al., 2008; Moyer, 1968; Siegel & Victoroff, 2009). Mental illness, prolonged stress, poverty, and drug abuse are common factors that contribute to the higher rate of violence or aggressive outbursts (Gowan, Swann, Moeller, & Lane, 2010; Moffitt et al., 2008; Moss, Yao, & Panzak, 1990; Siegel & Victoroff, 2009; Weinshenker & Siegel, 2002). In vulnerable individuals, stress in particular, can lead to a subtype of depression characterized by anger, anxiety, and aggression (Barnett, Fagan, & Booker, 1991; Weinshenker & Siegel, 2002). Stress might be a strong factor that can precipitate aggression and predicts the severity of developing violent behavior (Barnett et al., 1991).

The major limitation in the study of aggression is the lack of suitable animal models with predictive validity of human aggression that can provide insight into the neural mechanisms underlying the disorder, as well as new targets of therapeutic intervention (Blanchard & Blanchard, 2003; Gowan et al., 2010; Moffitt et al., 2008; Miczek, Fish, De Bold, & De Almeida, 2002; Miczek, Weerts, Haney, & Tidey, 1994). The use of antipsychotics in the treatment of aggression is limited by serious adverse effects, which necessitate the search for agents that can selectively reduce aggression without affecting other behaviors or causing any serious unwanted side effects. Current research is now focused on the development of serenics (compounds with selective anti-aggressive activity) that stimulate specific subsets of 5-HT receptors that are critically involved in the initiation and execution of aggressive acts (Miczek et al., 2002; Moffitt et al., 2008). However, the complex neural mechanisms and lack of a unified classification scheme for the categorization of human aggression has contributed greatly to the slow pace in the development of specific anti-aggressive agents (Weinshenker & Siegel, 2002). The aim of this review is to discuss the types, neurochemical bases, and animal models of aggression, with an appraisal of the pharmacological approach to the treatment of the disorder.

2. Types of aggression

The lack of a unified classification scheme for the categorization of human aggression has contributed greatly to the slow pace in the development of new medicines with specific anti-aggressive properties (Weinshenker & Siegel, 2002). Various types of aggression have been described in literature based on the factors that trigger it. Moyer (1968) classified aggression into the seven different categories: (1) Fear-induced aggression: This occurs when the animal is placed in a position where escape is denied and turns, instead, to attack a second animal perceived as a threat. (2) Maternal-induced aggression: This is a form of an attack that occurs when an animal is placed close to its young ones and a second animal approaches. (3) Intermale-induced aggression: An attack occurring by a male toward another male, but not a female, in its immediate environment. (4) Irritable aggression: An attack occurring in response to a threat, intimidation, or to an environmental condition which is irritating. (5) Sex-related aggression: In humans, sexual arousal is frequently associated with increased levels of hostility or hostile fantasies. In animals, components of aggressive behavior are sometimes associated with sexual acts. The aggressive and sexual aspects appear as components of the same behavioral act, thus, creating difficulties in classifying these behaviors. (6) Territorial aggression: An attack occurring when an intruder enters into an area that an animal has determined for itself as being its own domain. This is commonly known as a resident–intruder model. Most often, tests involving the resident–intruder model utilize animals of the same species although a resident animal might also attack an intruder of a different species (Moffitt et al., 1998; Weinshenker & Siegel, 2002). (7) Predatory aggression: Specifically triggered by the presence of a prey within the visual field of the predator; this response can be elicited in experimental conditions by stimulating the lateral hypothalamus of the cat (Siegel, Roeling, Gregg, & Kruk, 1999). The response is characterized by stalking of an anesthetized rat, which is followed by a bite to the back of its neck, which continues until stimulation is terminated (Siegel et al., 1999). It is evident that all these forms of aggression are meant for the dual purposes of survival and reproduction whether for obtaining food, access to a mate or protection. However, the central question that may be asked is whether these aggressive behaviors are related by a common neural mechanism or to different mechanisms underlying them.

2.1. Bimodal classification of aggression

A number of investigators have attempted to classify aggressive behavior in animals or humans into affective defense and predatory attack (Weinshenker & Siegel, 2002). Affective defense is an aggressive response based on the presence of fear and/or threat, which may be real or perceived. Predatory attack has been understudied relative to affective defense, and consists of a purposeful and goal-directed attack with the absence of sympathetic arousal (Weinshenker & Siegel, 2002). Thus, the seven types of aggression belong to one of two categories, predatory attack or affective defense behavior (Eichelman, 1985; Malone et al., 1998). All categories of aggression that include fear-induced, maternal, intermale, sex-related, irritable, and territorial appear to have a similar common feature, namely an aggressive response based on the presence of elements of fear and/or threat that may be real or perceived. Thus, these categories of aggression may be classified as affective defense (Weinshenker & Siegel, 2002). The motivation frequently triggering aggressive responses may be pain, a threat of another organism of the same or different species, and territory perceived by the animal in question as its own (Malone et al., 1998). Moyer showed the unique characteristics associated with affective defense, which are submission and appeasement, together with their associated postural positions. Moreover, these forms of behavior have been clearly described in different species, including mice, rats, cats, dogs, and primates. Moyer argues that submission reflects an aggression-inhibiting mechanism that has survival value by signaling to the dominant animal that the fight is over (Weinshenker & Siegel, 2002). In addition, the posture adopted by the defeated animal makes it difficult for the dominant animal to continue its aggressive acts. The
ultimate goal is that the fighting is terminated, thereby preventing further injury to the defeated animal (Weinshenker & Siegel, 2002).

Predatory attack, in contrast to affective defense, is limited to a single category of aggressive behavior. Predatory aggression is typically interspecies while others are expressed as intranspecific in interactions. Predatory behavior has been studied most extensively in the cat where this response can be elicited by electrical stimulation of the lateral hypothalamus (Weinshenker & Siegel, 2002). An experiment using a rodent model of predatory attack has also been described (Sandnabba, 1995). It is believed that predatory attack should not be regarded as a form of aggression, but rather as a behavioral strategy associated with feeding behavior (Adams, 1980; Weinshenker & Siegel, 2002). However, in humans, affective and predatory components of aggression may appear together.

In the literature, aggression has been classified into two subtypes: instrumental and emotional aggression. Instrumental aggression is considered harm with a purpose (Weinshenker & Siegel, 2002). It is a harmful behavior used specifically to obtain something desirable. Aggression caused by self-defense falls into this category. It is used to obtain the desired goal of self-preservation. Emotional aggression is the act of “inflicting harm for its own sake” (Weinshenker & Siegel, 2002). Revenge is a type of emotional aggression, and people attempt to enact revenge because of the pleasure they derive from the act itself. Emotional aggression is referred to as reactive or affective aggression in some sources (Malone et al., 1998; Weinshenker & Siegel, 2002).

However, the distinction of aggression into offensive and defensive behaviors appears to receive a wider acceptance, with well-defined brain mechanisms (Malone et al., 1998). Offensive behavior is characterized by the initiative of the aggressor and with the intent to cause damage to the opponent (Malone et al., 1998; Weinshenker & Siegel, 2002). In contrast, defensive behavior lacks active approach (initiative), and the defensive animal inflicts no intentional damage.

Predatory aggression represents a separate classification of aggression that seems to be primarily driven by appetite mechanisms and apparently has a distinct brain system involved (Malone et al., 1998; Malone et al., 1998; Weinshenker & Siegel, 2002). In the framework of evolution, these behaviors are meant to encourage survival of the fittest, to disperse populations, to aid adaptation to threatening environments, and generally to improve the probability of individual and species survival (Weinshenker & Siegel, 2002).

3. Neurochemical basis of aggressive behaviors

The neural mechanism that mediates aggression is still poorly understood even though several neurochemicals are implicated in the pathogenesis of this behavioral trait. Serotonin, or 5-hydroxytryptamine (5-HT), is the major neurochemical implicated in aggression and violent crimes. It has been shown to play a key role in the initiation, execution, and treatment of aggressive acts (Berman, Tracy, & Coccaro, 1997; Gowin et al., 2010). Several studies have confirmed a negative correlation between serotonin levels in the brain and aggression (Adams, 1979; Berman et al., 1997; Gowin et al., 2010). The negative correlation between serotonin turnover and aggression is commonly known as the serotonin-deficiency hypothesis of aggression (Berman et al., 1997). According to this hypothesis, aggression is characterized by low brain 5-HT levels (Berman et al., 1997; Brown et al., 1982; de Boer & Koolhaas, 2005).

3.1. Serotonin deficiency hypothesis of aggression

The original serotonin deficiency hypothesis was based on a negative correlation between trait-like impulsive aggression/violence and the CSF concentration of the 5-HT metabolite in humans and other primates (Berman et al., 1997; Brown et al., 1982). In humans, low levels of the serotonin metabolite (5-HIAA) in the cerebrospinal fluid have been associated with aggression and other forms of antisocial behavior, including assault, arson, murder, and child abuse as well as in violent forms of suicide. Moreover, a substantial number of non-primate animal studies have revealed that the propensity to exhibit excessive and abnormal forms of aggression is similarly linked to long-term reduced brain 5-HT activity (Miczek et al., 2002). In addition, studies have shown that chronically lowering or heightening brain 5-HT provokes increased or reduced levels of aggressive behavior respectively, further supporting the serotonergic deficiency hypothesis of aggressive behavior (Blanchard & Blanchard, 2003; Weinshenker & Siegel, 2002).

Initially, the association was found in isolated mice that became aggressive while reducing their 5-HT turnover, an indicator of 5-HT neurotransmission and consequent degradation (Garattini, 1967; Giacalone, Tansella, Valzelli, & Gurattini, 1968). Similar studies in humans and non-human primates confirm a negative correlation between serotonin turnover and aggressive tendencies (Brown et al., 1982; Miczek et al., 2002).

3.2. Factors regulating 5-HT levels and aggressive tendencies

The neural activity of serotonergic system depends on the integration of several processes that involve 5-HT synthesis, release, reuptake, degradation and receptor activation. Changes in any one or more of these processes might be responsible for the reduced 5-HT metabolites seen in aggressive and violent individuals. Thus, these sites might serve as targets for development of drugs for the control of aggression. Diets which are low in tryptophan, a precursor of serotonin which acts to increase its concentrations in the brain, have been shown to increase aggression in animals and humans (Cleare & Bond, 1995). The relevance of the serotonergic pathway in violent behavior is further supported by the ability of para-chlorophenylalanine, an irreversible inhibitor of 5-HT biosynthesis to heighten aggression in animals (de Boer & Koolhaas, 2005; Conner, Stolk, Barchas, Dement, & Levine, 1970; Valzelli, Bernaconi, & Gurattini, 1981; Vergnes, Depaulis, & Boehrer, 1986). Further, a single nucleotide polymorphism in the coding region of tryptophan hydroxylase, the enzyme for 5-HT synthesis gene, resulted in anger and aggression in healthy humans (de Boer & Koolhaas, 2005). The level of serotonergic activity is strongly regulated by 5-HT 1A/B receptors and may, therefore, play crucial roles in the mediation of aggression and violent behavior (Pineyro & Blier, 1999). The 5-HT 1A/B receptors are located pre-synaptically as autoreceptors on the soma and dendrites of serotonergic neurons, as well as post-synaptically on non-serotonergic neurons in several cortico-limbic areas that receive 5-HT terminals (Pineyro & Blier, 1999). Activation of somatodentritic 5-HT 1A/B autoreceptors by 5-HT or 5-HT 1A/B agonists has been shown to potently decrease the rate of firing of 5-HT neurons and decrease the rate of 5-HT synthesis and release or turnover (de Boer & Koolhaas, 2005; Pineyro & Blier, 1999). The 5-HT 1A/B agonists were found to exert potent anti-aggressive activity, which indicates the important inhibitory role for these receptors in the motivation or execution of aggressive acts (de Boer & Koolhaas, 2005; Pineyro & Blier, 1999).

The extracellular levels of 5-HT also depend on its reuptake and metabolic degradation by monoamine oxidase (MAO) enzymes. Serotonin selective reuptake inhibitors (SSRIs), which increase the availability of serotonin in the brain and are used commonly for the treatment of depression, were also effective for the treatment of aggression (Olivier, Mos, van der Heyden, & Hartog, 1989). The depletion of MAO-A gene in rodents produced an increase in aggressiveness (Cases et al., 1995). These findings indicate that availability of 5-HT at the synapses influences aggressive behavior.

3.3. 5-HT receptors relevant in aggressive behavior

The effects of serotonin in the nervous system are mediated by a family of different 5-HT receptor subtypes, many of which contain distinct subunits and differ in their mechanism of signal transduction.
Although studies have shown inverse relationship between 5-HT levels in the brain and aggressive behavior, the roles of 5-HT receptor subtypes in aggression are yet to be clearly elucidated. Pharmacological investigations and the use of knockout approaches in rodents revealed that 5-HT₁ and 5-HT₂ receptors, and their respective subtypes are more relevant in the expression of aggressive behavior (de Boer & Koolhaas, 2005; Pineyro & Blier, 1999).

Animal studies have shown that the use of specific agonists especially for 5-HT₁ receptor subtypes leads to a reduction in aggressive behavior (de Boer & Koolhaas, 2005). Conversely, inhibition of 5-HT₁ receptor subtypes using specific antagonists generally promotes aggression, although this relationship is not very consistent (Pineyro & Blier, 1999; de Boer & Koolhaas, 2005). The 5-HT₁A receptors that regulate serotoninergic system have shown to be more relevant in the mediation of aggression and violence (de Almeida & Miczek, 2002; de Boer & Koolhaas, 2005; Pineyro & Blier, 1999). The 5-HT₁A agonists exert potent anti-aggressive activity (de Boer & Koolhaas, 2005; Gowin et al., 2010), but a number of 5-HT₁A antagonists also decreased aggression (Mendoza et al., 1999). Such a discrepancy may be the result of these agents interacting with either pre- or post-synaptic 5-HT₁A receptors, other 5-HT receptor subtypes, or other neurotransmitter systems (Sanchez, Arnt, Hyttel, & Moltzen, 1993).

Regarding the 5-HT₁B receptor, knockout mice lacking this gene display heightened aggression compared to wild-types, indicating an important role for this receptor subtype in the mediation of aggression (Saudou et al., 1994). Activation of 5-HT₁B receptors inhibits aggressive behavior despite decreasing serotonin tone; presumably the behavioral effects of 5-HT₁B-receptor activation reflect modulation of other neurotransmitter systems (de Boer & Koolhaas, 2005).

The effect of 5-HT₁A and 5-HT₁B receptors in the control of 5-HT tone and vice versa aggression suggests that there are other 5-HT receptors that might be playing a crucial role in violent behavior.

Studies have also shown that there is reduced functionality of post-synaptic 5-HT₁A/C heteroreceptors in aggressive individuals (de Boer & Koolhaas, 2005). Studies examining the effect of the 5-HT₂ receptor reveal that the selective 5-HT₂A/C agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane decreases aggression at high doses, but also elicits a characteristic side effect of 5-HT stimulation termed “wet dog shaking” (Sloviter, Drust, & Conner, 1978). However, the relationship is not as clear with 5-HT₂ receptors, as several studies have shown conflicting results. While Sanchez et al. (1993) report no effects of 5-HT₂ antagonists on aggression, studies by White, Kucharik, and Moyer (1991) and Olivier, Mos, van Oorschot, and Hen (1995) provide evidence that the specific 5-HT₂ receptors reduce aggression. Antagonism of 5-HT₂ receptors appears to decrease aggression in animal models, and this effect may explain the ability of newer antidepressant agents (which, unlike the older medications, block 5-HT₂ receptors) to produce a reduction in aggression and agitation independent of effects on psychotic symptoms (Buckley et al., 1995). Studies suggest that the overall frequency of assaults, use of seclusion, mechanical restraint, and chemical restraint in patients with schizophrenia who are treated with clozapine are reduced over traditional neuroleptics (Ratey, Leveroni, Kilmer, Gutheil, & Swartz, 1993).

The presence of 5-HT₃ receptors in the amygdaloid complex and cerebral cortex suggests that these receptors may play potential roles in the mediation of aggression (Tecott, Maricq, & Julius, 1993). 5-HT₃ receptors are involved in fast-excitatory activities that are crucial in emotional and behavioral responses, as well as in other, less defined functions such as sensory perception, memory, and motor control (Tecott et al., 1993). White et al. (1991) and Sanchez et al. (1993) examined the effects of 5-HT₃ receptor antagonists, ondansetron, and zacopride in rodent inter-male aggression. They concluded that these compounds have no effect on aggression. The continued discovery of 5-HT₃-receptor subtypes indicates that further study will be needed to clarify the specific roles of the various receptor subtypes and their interactions in aggression. Nelson and Trainor (2007) emphasized the need to examine aggressive behavior in knockout mice that lack other 5-HT-receptor subtypes, as well as in tissue-specific 5-HT-receptor knockout mice, to discriminate between pre- and postsynaptic effects of 5-HT signaling aggression.

3.4. Other major neurochemicals implicated in aggression

The reciprocal interactions of serotonin with other several transmitters and hormones provide further evidence that this indolamine mediates impulsive aggressive behavior. The ultimate effect of serotonin on aggressive behavior appears to be related to its actions on several transmitter substances (Nelson & Trainor, 2007). The other major neurochemicals linked to aggression include gamma-aminobutyric acid (GABA), glutamate, dopamine, and noradrenaline (Nelson & Trainor, 2007). Neuroadaptive changes in dopamine, GABA, glutamate, and noradrenaline have been found after repeated aggressive experiences, both in the perpetrator and in the victim (Nelson & Trainor, 2007). However, agents that affect these neurochemicals are known to cause serious side effects, which tend to limit their usefulness in aggression (de Almeida et al., 2005).

3.4.1. GABA and glutamate

Gamma-aminobutyric acid (GABA) is the primary mediator of inhibitory transmission in the mammalian central nervous system. GABA is involved in the modulation of aggression and studies have shown low levels of this transmitter in aggressive individuals. Thus, it may be expected that substances that potentiate GABAergic neurotransmission should reduce aggressive activity (de Almeida et al., 2005; Miczek et al., 2002). Allosteric modulators of GABAₐ receptors, such as benzodiazepines and barbiturates, influence aggression levels in rodents, with an inverted U-shaped dose–response curve; low doses evoke aggression, whereas high doses reduce aggressive behavior (Gowin et al., 2010; Miczek et al., 2002). The facilitative effects of alcohol on aggression are well known, and also occur through allosteric modulation of GABAₐ receptors. Alcohol increases the duration and frequency of opening of chloride ion channels and thereby enhances GABA mediated chloride flux. GABA-receptor agonists reduce aggression in many people, presumably by reducing arousal (de Almeida et al., 2005; Gowin et al., 2010). Drugs which act on these systems, such as barbiturates, benzodiazepines and morphine, reduce arousal as well as aggression.

Glutamate is an excitatory amino acid that has been implicated in the genesis of aggression and violent behavior. Glutamate by increasing neuronal excitation may contribute to an increase in aggression, and is implicated in the expression of defensive rage behavior and in exaggerated emotional reactivity (Haller, Makara, & Kruk, 1998). Compounds with inhibitory effect against glutamate NMDA receptors may exhibit a nonspecific effect on aggression, mainly due to sedation.

3.4.2. Dopamine

The mesocorticolimbic dopaminergic neurons are involved in the mediation of aggressive behavior and also contribute to other motivated behaviors, such as reproductive and maternal behaviors, as well as food and drug intake. The D₂-receptor antagonist haloperidol has been used effectively for decades to treat aggressive patients, especially those with psychotic disorder (de Almeida et al., 2005). However, haloperidol has sedating and locomotor-impairing effects, which make it and other D₂-receptor antagonists unattractive for long-term treatment of aggression (de Almeida et al., 2005). Antagonists of both the D₁ and D₂ receptors have greater propensity to cause impairment of sensory motor performance (de Almeida et al., 2005). Dopaminergic receptor agonists have been shown to induce defensive behavior in cats and increase level of dopamine precedes the attack and defensive behavior in cats and amphetamine-induced dopamine release can increase aggression in rodents (Nelson & Trainor, 2007). However, the role of dopamine in the control of aggression still remains speculative (de Almeida et al., 2005).
3.4.3. Noradrenaline

Noradrenaline is involved in many functions, which are critical in the regulation of mood and behavior. Although no consistent relationship between noradrenaline and aggression has been established, pharmacological manipulations of noradrenaline levels or specific noradrenergic receptors indicate that noradrenaline signaling facilitates aggression (Nelson & Trainor, 2007). Norepinephrine’s relationship with aggressive behavior may best be explained in terms of the stress–response system and the type of aggressive behavior elicited (Koolhaas et al., 1999). Agonistic encounters are generally perceived as stressful and arousing that lead to elevated levels of noradrenaline, both centrally and peripherally (Haller et al., 1998). Noradrenaline may affect aggression on three different levels: the hormonal level, the sympathetic autonomous nervous system, and the central nervous system (CNS), in different, but functionally synergistic ways. Part of these effects may arise in indirect ways that are by no means specific to aggressive behavior; however, they are functionally relevant to it (Nelson & Trainor, 2007). Other effects may affect brain mechanisms specifically involved in aggression. Hormonal catecholamines (adrenaline and noradrenaline) are involved in metabolic preparations of the organism for the prospective fight; the sympathetic system ensures appropriate cardiovascular reaction, while the CNS noradrenergic system prepares the animal for the prospective fight (Haller et al., 1998; Nelson & Trainor, 2007). The major indirect CNS effects include decrease in pain sensitivity; and the enhancement of memory, which is very relevant for the survival of the animal.

Amphetamine usage has also been linked with increased aggression and this is probably because its major action within the brain is to facilitate the release of pro-aggression neurotransmitters such as noradrenaline and dopamine. The α- and β-adrenergic-receptor subtypes have been shown to mediate aggressive effect of noradrenaline (Haller et al., 1998).

4. Animal models of offensive aggression

The development of animal models that mimic specific aggressive disorders could lead to additional insights into the mechanisms that underlie aggression and treatment options. There are two major types of animal models of aggression: offensive and defensive aggressive paradigms (Adams, 1979; Malone et al., 1998; Weinschenker & Siegel, 2002). Models of offensive aggression include isolation-induced aggression, resident–intruder paradigm, and maternal aggression (Adams, 1979; Malick, 1979; Valzelli, 1973). Defensive aggression models include the characteristic of the lack of an active approach, and usually no wounds are made on the attacker (Adams, 1979; Bond & Lader, 1988). Examples of this model are foot shock or pain induced aggression, and the resident–intruder paradigm or maternal aggression in response to an intruder (Malick, 1979; Valzelli, 1973). Therefore, this kind of defensive behavior model reflects a different form of aggression than the offensive aggression models. Defensive aggression models have not been as extensively used in drug development, perhaps because they are viewed as less “pathological” (Malone et al., 1998; Weinschenker & Siegel, 2002).

4.1. Isolation-induced offensive aggression

Isolation-induced aggression in mice is an animal model of offensive aggression with strong predictive validity toward human aggression (Malick, 1979). A manipulation often used to induce aggression is isolation of male animals, typically mice, for several weeks. Many such isolated animals, on encountering another male, will exhibit attack behavior (Malick, 1979). The test is commonly conducted in the home cage of the isolated male mouse. However, performing the test in a neutral arena is more attractive because the situation delivers a mix of offensive, defensive and flight behaviors, which are not seen or are infrequently seen in the home cage confrontation (Olivier & Van Dalen, 1982).

The effects of several drugs including benzodiazepines, neuroleptics, psychostimulants, alcohol, 5-HTα1A-receptor agonists, serenics (5-HTβ1A/1B-receptor agonists), and selective serotonin reuptake inhibitors have been investigated in this model (Miczek, DeBold, van Erp, & Tornatzky, 1997). Benzodiazepines show inverse U-shaped dose–response curves in this model. Benzodiazepines at low doses, produced increases in aggression, whereas at high doses, decreases are observed (Miczek et al., 1997; Olivier & Van Dalen, 1982). Psychostimulants enhanced locomotor activity thereby interfering with the normal agonistic behavior (Miczek et al., 1997). Amphetamine, a psychostimulant, produced no effect on aggression, but it decreased the locomotor threshold, indicating its stimulatory action without having specific effects on aggression (Miczek et al., 1997). Antipsychotics, chlorpromazine, and haloperidol exert antiaggressive effect, but also caused nonspecific effects such as impairment of sensorimotor performance (Miczek et al., 1997). However, serenics (serotonergic 5-HTβ1A-receptor agonists) exhibited a highly selective antiaggressive activity, reducing aggression specifically without affecting other behaviors or causing any unwanted side effects (Olivier, Mos, Hartog, & Rasmussen, 1990).

4.2. Resident–intruder offensive behavior

The resident–intruder model is a unique animal paradigm for different aspects of social interactions and also provides an excellent predictive validity toward human aggression (Miczek, 1974; Olivier & Van Dalen, 1982). Human aggression is often associated with complex interpersonal interactions, and the resident–intruder interaction model may be relevant to predict what drugs may do in humans. The resident–intruder paradigm is a widely used model in psychopharmacology and employs the resident animal’s response to a conspecific intruder (Koolhaas, Schuurman, & Wiepema, 1980; Miczek, 1974). In this paradigm, a male rat or mice is housed with a female, a situation resembling the natural situation in which animals establish and defend territories. When resident or territorial males meet an unfamiliar male intruder in their territory, heavy fighting may ensue, considered natural fighting (Miczek, 1979). Aggressive behavior in this situation may consist of patrolling, approach, investigation, threats, fighting, chasing, and dominant posturing (Koolhaas et al., 1980). The nature of such interactions between an attacking resident and an opponent varies with the quality of the intruder, especially age and hormonal status, and the resident’s experience (Koolhaas et al., 1980). The types of behaviors displayed by the resident toward the intruder are not random but follow certain rules, a strong indicator of the neural substrates involved (Adams, 1979; Koolhaas et al., 1980; Olivier et al., 1984). The resident–intruder model differs both from isolation induced aggression in mice because there is no isolation, which may lead to behavioral abnormalities (Valzelli, 1973). Moreover, resident–intruder paradigms have a very wide species generality including humans (Miczek, 1979). This model discriminates effectively the quality and behavioral mechanisms of action of several drugs with proaggressive and anti-aggressive actions (Mos, Olivier, & Tulp, 1992). Both proaggressive (alcohol and benzodiazepines) and anti-aggressive effects of psychoactive drugs are highly similar in rodents and humans (Olivier et al., 1984). Benzodiazepines at low doses enhance aggression, whereas at higher doses they clearly cause ataxia, which interferes with behavioral performance (Olivier et al., 1984). Neuroleptics, like psychostimulants, alter the display of agonistic behavior although in different ways. Serenics display a highly specific anti-aggressive profile without interfering with other behavioral functions (Mos et al., 1992; Olivier et al., 1984).

4.3. Offensive behavior induced by electrical brain stimulation

This offensive behavior is similar to that of offensive territorial males and can be elicited by electrical stimulation in the hypothalamus of rats.
(Kruk, Van der Poel, & De Vos-Frerichs, 1979). Stimulation of the hypothalamus is accompanied by an increase in levels of stress hormones (adrenocorticotropic hormone, corticosterone, and prolactin) and not caused by the stress of fighting (Kruk et al., 1998). This behavior is readily reproduced under controlled circumstances, thereby meeting an important requirement for a model to study aggression. Depending on the stimulus intensity, extreme forms of offensive attack and severe damage to the opponent can be produced (Kruk et al., 1979). In addition to aggressive behavior, stimulation in this area of the hypothalamus also stimulates other behaviors, including locomotion and teeth chattering (Van der Poel et al., 1982), thereby allowing for the determination of the specificity of drug action (Koolhaas, 1978; Kruk et al., 1979). In this paradigm, the effects of drugs are measured by the changes in the current thresholds required to evoke the respective behavior (Van der Poel et al., 1982). Increases in the current thresholds for aggression indicate anti-aggressive effects, considered specific if simultaneously the drug does not affect thresholds for locomotion (Siegell et al., 1999). This hypothalamic-induced aggression model is highly relevant for modeling certain kinds of human aggression (Koolhaas, 1978; Kruk et al., 1979). By directly stimulating neural substrates in the brain involved in offensive aggression, this model has great potential to predict violent and pathologic aggression in humans (Siegell et al., 1999). In contrast to the more natural models (isolation-induced, resident-intruder, maternal aggression), this model is not sensitive to certain intervening variables present in the other paradigms (anxiety, fear, sedation, and motor and sensory disturbances) and directly reflects anti-aggressive properties of drugs (Siegell et al., 1999).  

4.4. Maternal aggression

Although aggression is often considered a male-related phenomenon, females can be quite aggressive under certain conditions, such as in hypothalamically induced aggression in rats (Kruk et al., 1984) and maternal aggression in several rodent species (Mos et al., 1987). The use of a female aggression paradigm to model human aggression is quite uncommon in psychopharmacology. The maternal aggression has clear neural and hormonal determinants and is highly purposeful, providing protection to the offspring. The maternal aggression paradigm is based on the finding that a lactating female rat or mouse with pups exhibits offensive behaviors toward a wide variety of intruders (Mos et al., 1987). This behavior is most pronounced during the first part of the lactating period (Erskine, Barfield, & Goldman, 1978). The critical stimulus depends on the proximity of some threatening object to the female’s young ones (Moyer, 1968). However, the behavior of the lactating female toward the intruder is clearly self-initiated, proactive, and not necessarily reactive to any threat initiated by the intruder. Although the paradigm is labor-intensive and needs extensive planning, several psychoactive drugs have been tested in it and have led to a model with a comparable predictive validity as the male offensive paradigms in rodents (Erskine et al., 1978). Although the patterns of the aggressive behavior of the attacking female are different from male aggression, the effects of several classes of drugs were shown to be similar to those found in the male paradigms (Erskine et al., 1978).

5. Animal models of defensive behaviors

Defensive behaviors are forms of agonistic behavior, which are characterized by submission, flight, and similar reactive behaviors. Fighting, when it occurs in a defensive animal, is merely a reaction to an attack. The defensive behaviors such as flight or submission are apparently intended to escape from or prevent further agonistic interactions (Koolhaas et al., 1980). Some of the drugs such as the neuroleptics with anti-offensive activity are known to impair the defensive and flight reactions of the animals (Koolhaas et al., 1980).

5.1. Defensive behavior in resident–intruder paradigm

The behavior of an intruder in the resident–intruder or maternal aggression is a more natural model for assessing effects of drugs on defensive behavior. Defending animals in these paradigms use special tactics to protect the more vulnerable parts of their bodies (Blanchard et al., 1998; Olivier et al., 1994). In unconstrained conditions, animals on the defense usually flee from the territory of the residential male or lactating female, but when this is impossible, as in laboratory conditions, they defend themselves by flight, crouching, upright defensive postures, emission of ultrasounds, and submissive postures (Koolhaas et al., 1980). Generally, these behaviors are aimed at protecting the back, the area where most wounds are inflicted by attacking rodents (Koolhaas et al., 1980).

Several drugs (neuroleptics, alcohol, benzodiazepines, or psychostimulants) that influence the sensory or motor capabilities of the intruder lead to changes in the defense or flight responses of the animals (Blanchard et al., 1998). Amphetamine enhances flight while haloperidol impairs defense or flight capability (Olivier et al., 1994). Serenics do not affect the defense or flight capabilities of the intruders, an effect in line with their specific anti-offensive qualities (Blanchard et al., 1998; Olivier et al., 1994). Pain or shock-induced defensive behavior is another paradigm used to study the effects of drugs on defense or flight capability of the animals. However, the behavior of the animal can be masked by analgesic drugs in this model (Olivier et al., 1994). A useful application of foot shock-induced defense behavior is to determine specificity of anti-aggressive agents (Olivier et al., 1994). Neuroleptics and benzodiazepines inhibit foot shock-induced behavior due to muscle-relaxing effects (Olivier et al., 1994). Serenics (etoprazine, fluprazine, and others) do not inhibit this foot shock-induced behavior, indicating selective anti-offensive activity.

6. Limits to animal models

Although the use of animal models has shed some light on behavioral and neurobiological mechanisms of aggression, it is still difficult to relate these mechanisms to human violence. Fighting in animals, for example, consists of combinations of biting, wrestling and chasing, whereas aggression in humans can take both physical and verbal forms (Nelson & Trainor, 2007). Thus, this diversity tends to limit direct comparisons between species in components of aggression. Another major problem with animal models is that most aggression tests only assess the quantitative aspects of the aggressive encounters. Thus, better aggression tests are needed to assess the quality as well as the quantity of aggression, and to translate it onto human aggressive acts. Further, the studies of aggression in animals are conducted under controlled settings, thereby eliminating the variation in environmental factors that might have crucial effects on the behavior.

7. Pharmacological treatment of aggression

The major goal of aggression research is to develop pharmacotherapeutic agents that can be used to control human aggression and violence without impairing other behaviors. These research efforts are yet to yield specific compounds that can selectively reduce aggression in humans. The first attempt toward the treatment of aggressive behavior began in the mid-1970s with the use of lithium carbonate in prison inmates (Dostal & Zvolinsky, 1970; Sheard, Marini, Bridges, & Wagner, 1976). Lithium carbonate was shown to reduce impulsive aggression to extremely low levels during the course of treatment (Sheard et al., 1976). The mechanism by which lithium carbonate reduces aggression still remains unknown, but may involve enhancement of 5-HT neurotransmission and a dampening of catecholaminergic function (Campbell et al., 1995; Soares & Gershon, 1998). The
current pharmacological agents used in the treatment of aggressive behavior or violent outbursts target various neural mechanisms including dopamine receptors, the serotonin transporter, the beta-adrenergic receptor and GABA receptors (Miczek et al., 2002). Although these agents reduce aggression, they also interfere with other functions; therefore there is a need for improved and more selective therapies (Barrett, Edinger, & Siegel, 1990; Olivier et al., 1995; Buckley, 1999).

Dopamine receptor antagonists, such as chlorpromazine and haloperidol, have been used effectively for decades to treat aggressive patients, especially those with psychotic disorder (Olivier et al., 1990). The use of antipsychotics in the treatment of aggression is largely aimed at sedating patients with psychosis or to reduce the psychotic thinking that may trigger aggressive behavior. The propensity to cause sensorimotor performance or catalepsy has reduced the clinical utility of antipsychotics for long-term treatment of aggression (Olivier et al., 1990; Rabinowitz, Avnion, & Rosenberg, 1996). These drugs also affect the defense or flight capabilities of the organisms, which further limit their usefulness in aggression (Olivier et al., 1990). Although many atypical antipsychotics exhibit low tendency to cause sensorimotor performance, they also produce other unwanted side effects (Olivier et al., 1990). Drugs like barbiturates and benzodiazepines, which act through potentiation of GABA inhibitory neurotransmission, produce decreases in aggressive behavior, however, at high doses (Olivier et al., 1990). The anti-aggressive effect of these drugs is due to sedation or muscle relaxation (de Almeida et al., 2005; Navarro et al., 2004). The defense or flight capabilities of the organisms, is also impaired by these GABAmimetics, which further limit their use in aggression (Olivier et al., 1990).

The role of the central noradrenergic system in facilitation of aggression (Nelson & Trainor, 2007) suggests that agents with adrenergic blocking property should exhibit anti-aggressive activity. Indeed, adrenergic receptor blockers have been found effective in reducing aggressive behavior in patients with organic brain syndromes or chronic psychosis (Haller et al., 1998; Nelson & Trainor, 2007). Both propranolol and nadolol, which are beta adrenergic receptor antagonists, reduced aggressive behavior in chronic psychiatric inpatients, independent of psychiatric symptoms (Haller et al., 1998). However, the uses of these medications are limited by the side effects of hypotension and bradycardia (Nelson & Trainor, 2007).

Pharmacotherapeutics that may be more relevant in managing violent and aggressive individuals are those that specifically target 5-HT signaling mechanisms either through inhibition of 5-HT reuptake or modulation of 5-HT receptor systems (Coccaro, Kavourlis, & Hauger, 1997). The rationale to manage aggressive patients with 5-HT-enhancing agents is rooted in the consistent findings of an inverse relationship between 5-HT and aggression. Thus, the therapeutic strategies have been aimed toward enhancing 5-HT neurotransmission to correct or compensate for the putative deficiency (Coccaro & Kavourlis, 1997). Both preclinical and clinical studies have documented the efficacy of these agents, specifically with respect to the 5-HT selective reuptake inhibitors (SSRIs) in aggression (Coccaro Bond, 2000; Fuller, 1996). SSRIs have been shown to reduce verbal and physical aggression in patients with borderline personality disorder (Coccaro et al., 1997; Fuller, 1996). The enhancement of central 5-HT function by the SSURI is presumed to underlie their anti-aggressive effect in these patients (Coccaro et al., 1997; Fuller, 1996). However, the SSRIs cannot selectively reduce aggression, without affecting other behaviors or causing serious unwanted side effects (Coccaro & Bond, 2000; Fuller, 1996).

The pharmacological approach to the treatment of aggressive behavior or violent outbursts demands the use of agents that can interact with a subset of 5-HT receptors that are critically involved in the mediation of aggression. Current research effort is now focused on the development of agents that selectively reduce aggression by targeting specific subtypes of 5-HT especially 5-HT1A/B receptor and 5-HT2A/C receptors (Cleare & Bond, 2000). The 5-HT1A agonists have been shown to exert potent anti-aggressive activity without interfering with other behavioral functions (Summers et al., 2005). The 5-HT1A/B agonists, such as eltoprazine, zolmitriptan, anpirtoline, 5-methoxy-N,N-dimethyltryptamine, ipsapirone, and buspirone significantly reduce aggressive behaviors in a hostile confrontation (Bell & Hobson, 1994; Olivier et al., 1989). The pharmacological mechanism of action of these serenic drugs is generally explained by changes in 5-HT neuron function that heighten the effectiveness of serotonergic signaling at their postsynaptic receptor targets. These drugs also reduce the escalated aggression that often follows alcohol consumption, frustration, and social instigation (de Almeida et al., 2001; Fish, Facchidomo, & Miczek, 1999). The behaviorally selective profile of these agents suggests that 5-HT1A agonists might be attractive compounds for the control of aggression and violence (de Almeida et al., 2005; Mendoza et al., 1999; Sanchez et al., 1993; White et al., 1991). Although 5-HT2 receptor agonists caused a decrease in aggressive responses, they also elicit a characteristic side effect of 5-HT stimulation termed “wet dog shaking” (Sloviter et al., 1978). Antagonism of 5-HT2 receptors decreased aggression in animal models, and this effect may explain the ability of the newer antipsychotic agents (which, unlike the older generation, block 5-HT2 receptors) to produce a reduction in aggression and agitation (Buckley et al., 1995). Studies suggest that the overall frequency of assaults, use of seclusion, mechanical restraint, and chemical restraint in patients with schizophrenia who are treated with clozapine are reduced over traditional neuroleptics (Ratey et al., 1993). However, the efficacy and tolerability of selective 5-HT2 receptor antagonists on aggression are yet to be established.

8. Conclusion and challenges for future research

Although several mechanisms are involved in the expression of aggression, it is imperative that the precise neurochemical vulnerabilities be clearly defined and understood. It is a challenge for future research to elucidate how precisely these mechanisms interact to contribute to aggressive behavior. Further, animal studies of aggression typically measure aggressive behavior under a controlled single set of environmental conditions. However, expression of aggression in humans is subject to fluctuating physical and social environments. Thus, better aggression tests are necessary to assess the quality as well as the quantity of aggression in animals, and how to relate animal data to human aggression. Moreover, the continued discovery of more 5-HT receptor subtypes indicates that further studies may be needed to clearly define the specific roles of the various receptors and their interactions in aggression. The development of more specific 5-HT-receptor agonists and antagonists will also aid in the understanding of the basic mechanisms that underlie aggression. The major goal of aggression research is to develop interventions that could control human aggression. And current research efforts are directed toward the use of agents that can selectively reduce aggression by targeting specific subtypes of 5-HT receptors that are critical in the mediation of violent behavior.

References


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Clozapine as a specific aggressive control of aggression: Hormones, the peripheral sympathetic and central noradrenergic systems.


