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Animal models of excessive aggression: implications for human aggression and violence

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Escalated interpersonal aggression and violence are common symptoms of multiple psychiatric disorders and represent a significant global health issue. Current therapeutic strategies are limited due to a lack of understanding about the neural and molecular mechanisms underlying the 'vicious' shift of normal adaptive aggression into violence, and the environmental triggers that cause it. Development of novel animal models that validly capture the salient features of human violent actions combined with newly emerging technologies for mapping, measuring, and manipulating neuronal activity in the brain significantly advance our understanding of the etiology, neuromolecular mechanisms, and potential therapeutic interventions of excessive aggressive behaviors in humans.

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Introduction

Across the animal kingdom, aggression is the behavioral weapon of choice for individuals to gain and maintain access to desired resources (food, territory, mating partners), defend themselves and their progeny from rivals and predators, and establish and secure social status/hierarchical relationships. Clearly from a biological point of view, aggressive behavior is considered a highly functional form of social communication leading to active control of resources and the social environment, and thus is essential for individual and population survival and evolutionary preserved. It is characterized by a ritualized set of species-typical behaviors performed in close interaction with another individual (see Refs [1•] and [2] for more detailed descriptions of the various forms of aggression and the different aggressive acts and postures displayed in the commonly used resident–intruder aggression paradigm). Although most individuals engage in social conflicts with appropriate and well-controlled (functional) forms of aggressive behavior, a relatively small fraction of individuals can become excessively aggressive and extremely violent. In humans, this small percentage (ranging from 3 to 7%) of violent aggressive individuals is a major source of death, injury, social stress and ensuing disability, thus constituting one of the most devastating societal problems worldwide. These violent and pathological forms of aggression observed in our human society and clinically, co-morbid across a wide spectrum of DSM-V-defined psychiatric and neurological disorders, have motivated much of the scientific interest in aggressive behavior in animals. In particular, there is a need to understand these problematic behaviors in terms of their underlying causal mechanisms and modulating factors. Although once regarded as a typical human proclivity, lethal violence is also expressed in 40% of mammalian species and has significant phylogenetic roots [3•]. Therefore, animal models can be developed that captures the essential features of human violence and obtain experimental support of the causal nature of underlying molecular genetic mechanisms and environmental triggers.

Violence is the pathology of functional aggressive behavior

Although aggression is basically highly functional, it can be potentially harmful for both the victim and aggressor. Therefore, throughout the animal kingdom, strong inhibitory feedback mechanisms are operative such as taboos, ritualization, submission, reconciliation and appeasement to keep physical aggression in control and to prevent its potentially adverse (*i.e.*, injury or death) consequences. Yet, how these are embedded in neural mechanisms to gate the expression of aggression is largely unknown. Until a decade ago, most ethological studies of aggression have focused on the ultimate and proximate mechanisms of this normal adaptive aggressive behavior, while clinically the focus is predominantly on violent individuals and excessive or inappropriate forms of human aggressiveness. Actually, the lack of biologically relevant and valid animal models for these pathological forms of aggressive behavior is the main reason for the gap in our knowledge about the neurobiological roots and molecular genetic mechanisms of violence in humans. Therefore, new experimental animal models have been developed that focus more on provoking escalated and uncontrolled forms of aggressive behavior in order to capture the problematic clinical violent phenotype.

Basically, valid models should demonstrate excessive, injurious and impulsive aggressive behavior that exceeds and/or deviates from normal species-typical levels or patterns (see Refs [4–6,7•,8] for elaborate descriptions). In this view, violence can be defined as a pathological form of aggressive behavior that is not subjected to inhibitory control mechanisms and that has lost its function in social communication (*i.e.*, aggression out of proportion, control, and context). Hence, this loss of the social communicative nature of the aggressive interaction in the currently available animal models of escalated aggressive behavior are operationally characterized by five factors: (1) Low provocation threshold, short latency to initiate attack; (2) High rate and intensity, leading to significant tissue damage; (3) Disregard of appeasement signals, (4) Lack of species-normative behavioral structure (*i.e.*, attacks are deficient in conveying signaling intention and targeting opponent's body parts), and (5) lack of context in that critical features of the opponent such as age, sex or situation are misjudged [5,6,7•,8,9]. Several of these signs and symptoms of violent-like aggressive display are reliably engendered in the following animal models that have achieved, at least to a variable extent, similarity with human violent aggression in terms of symptomatology and phenomenology (face validity), phylogenetic and ontogenetic origins (construct validity), and response to clinically established treatments using clearly understood neurobiological mechanisms (predictive validity).

Current animal models of escalated, violent-like aggression

(1) Escalated aggressive behavior in unselected feral animals and selective breeding for escalated aggression

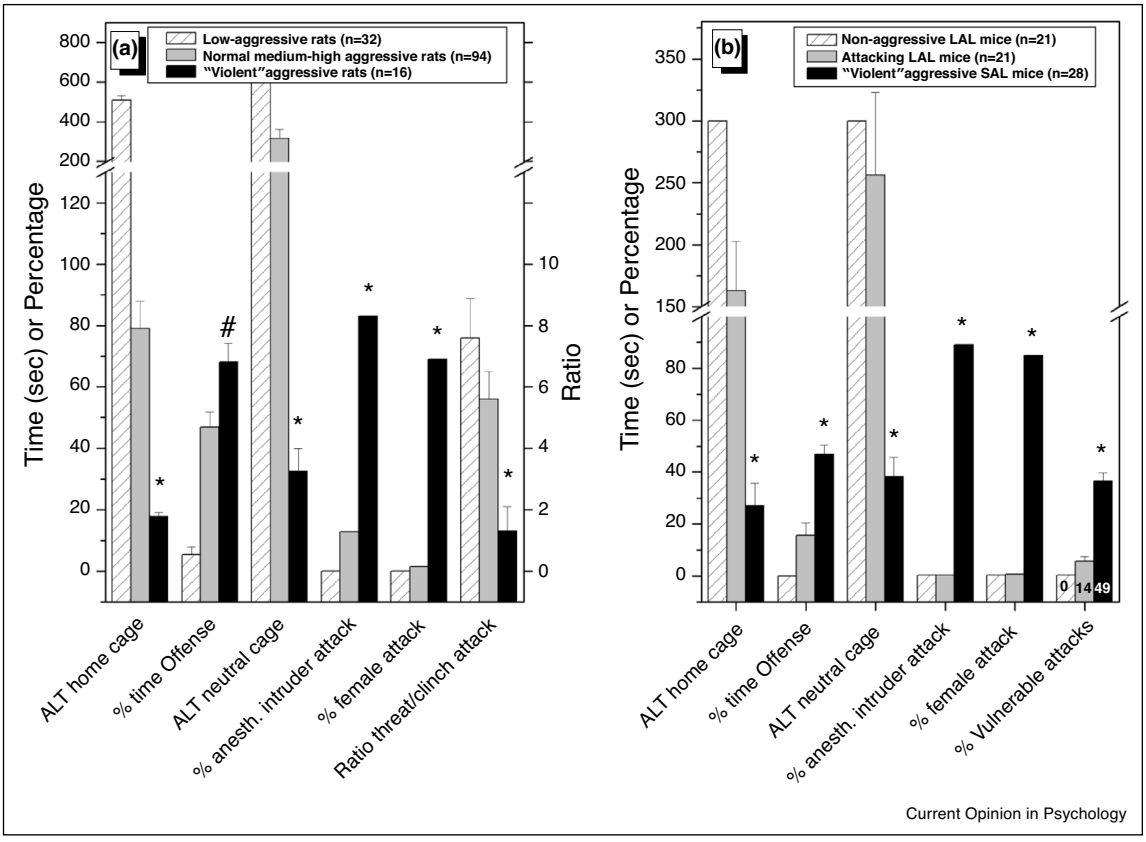
Compared to highly domesticated laboratory-bred conspecifics, feral rats and mice display much higher levels and broader ranges of innate and normal adaptive offensive aggression [10•]. More interestingly, escalated aggressive and violent characteristics can be engendered in approximately 8–12% of these constitutionally medium to high-aggressive individuals upon experiencing repeated victorious episodes of social conflict (Figure 1; [6,11,12]). Enhanced levels of offensive aggression and an increased probability of winning an aggressive encounter following previous victories (the so-called 'trained fighter' or 'winner' effect) have been demonstrated frequently in a wide variety of animal species [13].

Numerous studies in a wide variety of animal species have convincingly demonstrated that in addition to securing access to resources, the most intriguing consequence of winning an aggressive conflict is the self-reinforcing or rewarding effects. Actually, individuals seek out the opportunity to fight and engaging in aggressive behavior, even in the absence of threat-provoking cues. The most persuasive evidence that acts of aggression are rewarding is that animals will show operant learning for future aggression (*i.e.*, animals are willing to work, such as by pressing a bar for aggression [14]), and will exhibit conditioned place preference for a location associated with a previously successful aggressive encounter [15,16].

This feral animal model affords the opportunity to identify the dynamic molecular changes in the neural 'aggression' control circuits that are hypothesized to underlie the shift of normal adaptive aggression into inappropriate violent-like forms [6]. High-aggressive residents in comparison to low- or non-aggressive residents, show an increased number of activated (Fos-expression as a surrogate molecular marker for neural activity) neurons in medial and extended amygdala, ventrolateral portion of the Ventromedial Hypothalamus, Nucleus accumbens shell, orbital Prefrontal cortex, lateral/ventrolateral Peri-Aquaductal Gray and Dorsal Raphe Nucleus, whereas in the ventromedial Prefrontal Cortex, Lateral Septum and dorsolateral PAG a reversed pattern was seen [17,18]. This supports the view that a quantitatively different number of activated neurons within several nodes of the 'aggressive' brain Social Behavior Network (SBN, see below) underlie the different levels of expressed offensive aggressiveness. However, the extent to which similar or different sets of neurons within these brain regions are involved in the divergent levels and/or abnormal forms of aggression remains a challenging issue for future studies.

The functional activity of this neural network, and thereby the tendency to aggress more or less, is also determined by a wide variety of neurotransmitters such as the monoamines serotonin (5-hydroxytryptamine; 5-HT) and dopamine (DA), the 'social' neuropeptides oxytocin (OXT) and vasopressin (AVP), the 'stress' neuropeptide CRF, the 'stress' HPA- and 'sex' HPG-axis's steroid hormones (corticosterone, testosterone, estrogen) and their cognate receptors and intraneuronal signaling molecules. Indeed, high- and low-aggressive WTG rats or SAL/LAL mice show profound differences in the oxytocinergic innervation and modulation of the central nucleus of the amygdala [19], the vasopressinergic neurons in the bed nucleus of the stria terminalis and its innervation of the lateral septum [20] the striatal dopaminergic mechanisms, and particularly the auto-inhibitory control mechanisms of serotonin neurotransmission [6,12]. Notably, animals that escalate their aggressiveness demonstrate 5-HT_{1A} autoreceptor supersensitivity and diminished 5-HT reuptake functionality that may be the causative link in the cascade of neurochemical events leading to 5-HT deficiency characterizing these violent-like animals. Similar to excessively aggressive humans and other primate species, only violent-like feral rat and mouse subjects exhibit dysfunctional brain serotonergic neurotransmission (Figure 2; [6]). Capturing this

Figure 1



(a) Normal and violent-like aggressive behavioral characteristics in low-aggressive and medium-high aggressive WTG rats after multiple (>10) victorious experiences. **(b)** Generally similar violent-like aggressive characteristics are observed in artificially selected high-aggressive SAL mice after only 3–4 repetitive winning experiences. * Indicate significant differences from the other two groups.

neurochemical hallmark of pathological aggressiveness (serotonin deficiency) adds significantly to the face and construct validity of this model. The data also persuasively confirm the causal role of tonic 5-HT activity in setting a trait-like threshold for aggressive behavior. Increased understanding of the regulatory mechanisms for persistent 5-HT_{1A} autoreceptor gene expression and protein synthesis that are triggered by repeated victorious aggressive experiences promise to identify novel targets for specific pharmacotherapeutic intervention.

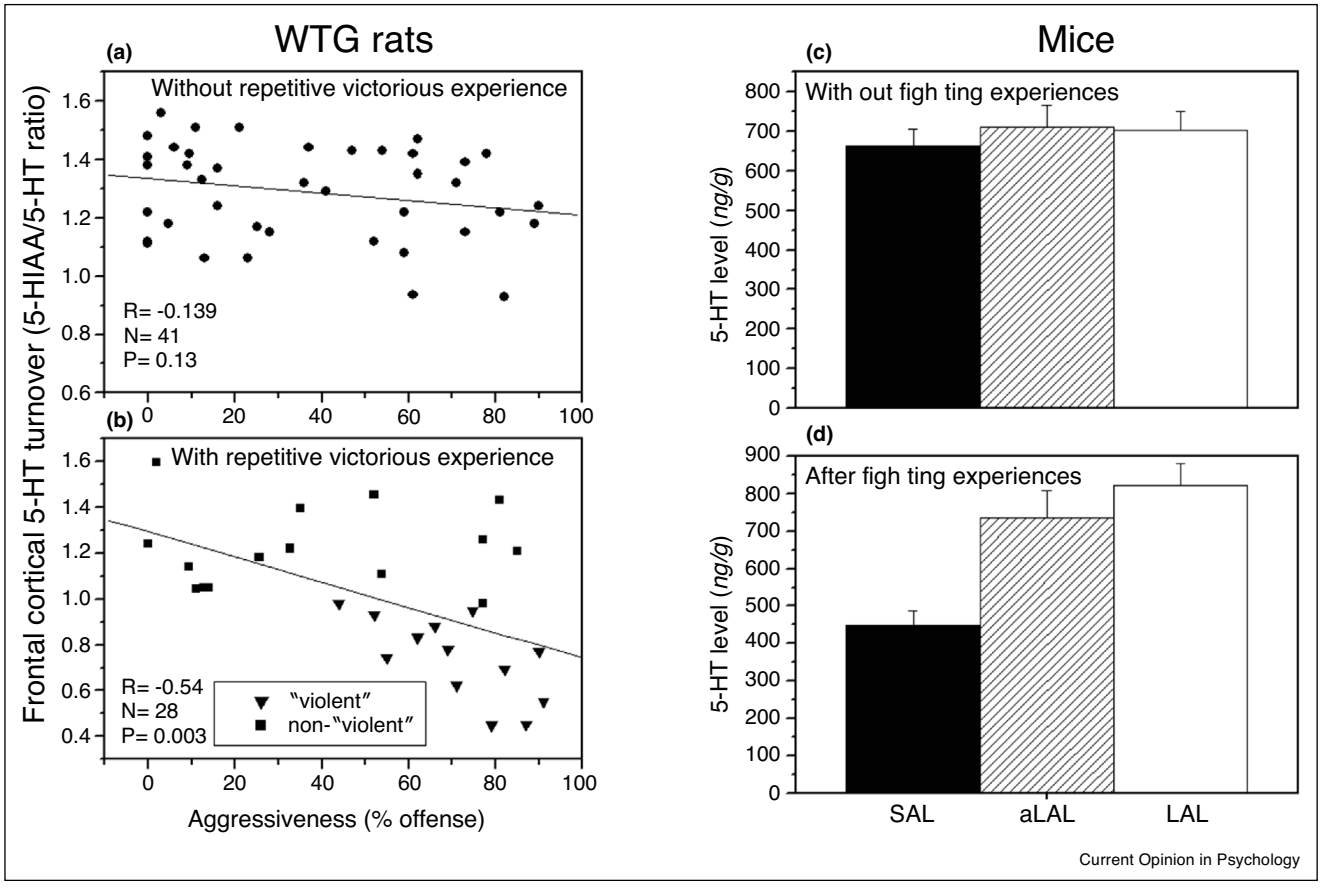
(2) Alcohol-heightened aggression

Among all psychoactive substances, alcohol is the most potent agent for promoting violent aggression and reduction of behavioral control in a subset of human individuals [21]. Acute low doses of alcohol, as well as withdrawal from long-term alcohol use, may lead to escalated aggressive behavior in a significant subgroup (approximately one-third) of individual mice, rats and monkeys [22]. Emerging pharmacological evidence from these alcohol-related aggression models point to major individual differences in the brain serotonergic and/or dopaminergic systems that play an important part in the biological vulnerability to increased alcohol-related aggressiveness. For example, trait-like reductions in frontal cortical serotonin functioning seem to mediate the increased propensity for alcohol-heightened aggression [23]. Furthermore, there is growing support for the hypothesis that the neural mechanism mediating alcohol's reinforcing/euphoric effects overlap or closely interact with those that are responsible for aggressive and violent acts that in themselves function as reinforcers. Therefore, (epi)genetic factors that moderate reward sensitivity may contribute largely to individual difference in alcohol-facilitated aggression. Recent evidence indeed demonstrated that OPRM1 genotype interacts with low brain 5-HT activity to predict alcohol-heightened aggression in primates [24].

(3) Abnormal 'predatory-like' aggressiveness in the hypoglucocorticoid rat

The development of the hypoglucorticoid model was prompted by the discovery that violent aggression in patients with antisocial personality disorder, psychopathy and conduct disorder is accompanied by a marked

Figure 2



Prefrontal cortex serotonin deficiency as a consequence of developing abnormal forms of 'violent'-like aggressiveness in WTG rats (left panels **(a)** and **(b)**) and artificially-selected house mice (right panels **(c)** and **(d)**). Note that 5-HT deficiency occurs in only those individuals (certain WTG rats and all SAL mice) that developed excessive and abnormal forms of aggressiveness after winning fights repeatedly. No 5-HT deficiency is present in fighting-naïve animals.

hypoarousal in terms of glucocorticoid production, heart rate, and skin conductance [25]. Glucocorticoid deficiency in rats, induced by adrenalectomy with low dose glucocorticoid replacement, considerably increases attacks aimed at vulnerable targets, diminishes intention signaling, disturbs social behavior, and reduces autonomic activation [5]. Intriguingly, the abnormal aggression in this model is associated with a marked activation of predatory aggression-related brain structures, for example, lateral/perifornical hypothalamus, central amygdala, ventrolateral aspects of the midbrain PAG [26] Thus, this animal model seems to capture the callous-unemotional hallmarks of psychopaths and conduct disordered patients, and may prove useful to establish the causal role of glucocorticosteroid hormones and its two cognate intracellular receptors in mediating these social dysfunctions.

(4) Early-life social isolation enhanced aggressiveness

Another interesting set of relevant animal models has recently been developed to capture the cardinal features of early-life adversity (*i.e.*, emotional neglect, loss of parents, child abuse) on hyper-aggressiveness and antisocial behavior in humans in order to study the underlying neuromolecular and (epi)genetic mechanisms [27,28]. Generally, early life stress in animals enhances adult anxiety-like behaviors and has a major impact on social and aggressive behaviors. In particular, post-weaning social isolation (PWSI) recapitulates early social neglect by eliminating social contacts with conspecifics from weaning into early adulthood. Rodents submitted to this paradigm show strong signs of social incompetence as adults and display abnormal and high levels of aggression, attacks on vulnerable body parts, sudden unsignaled attacks, and ambivalence between offensive and defensive behavior [29]. Like humans, these PWSI rats show exacerbated autonomic arousal and glucocorticoid stress responses. Furthermore, in line with human data, structural (reduced vascularization and thickness) and functional alterations in the prefrontal cortex were found in these deviant aggressive animals [30]. Clearly, early life stress and maltreatment (adverse rearing conditions) is an

important paradigm to study the neuromolecular and epigenetic mechanisms that underlie the (neuro)development of adult excessive aggressive behaviors.

(5) Brain hypothalamic stimulation-evoked attack

By employing numerous increasingly sophisticated tools of functional neuroanatomy (*i.e.*, from the classic electric/chemical lesion and stimulation techniques to neurochemical mapping and manipulations), a structurally and functionally highly interconnected 'social behavior neural network' (SBN; [31] has been revealed. This evolutionary ancient and conserved network functions as the core circuitry for the regulation of vertebrate social behaviors [32,33]. Nuclei within the hypothalamus, extended amygdala, lateral septum, periaqueductal gray, prefrontal cortex and mesocorticolimbic circuits that encompass this SBN are known to encode aggressive behaviors ([34,35] for a more detailed review). A challenging task is to decipher how the relative levels of activity of distinct sets of neurons within the various nodes of this basic SBN circuitry give rise to different phases (initiation, execution and termination), levels, and/or forms of aggressive behavior.

Among all nodes of the SBN, the hypothalamus is by far the best-studied region in relation to aggression ever since the seminal knife-cut lesion [36] and the intracranial electrical stimulation experiments [37] showing suppression and provoking, respectively, of raging aggressive display in cats. With the development of appropriate stereotaxic instruments, an extensive series of groundbreaking lesion- and electric stimulation studies mapped out this attack area in the hypothalamus, hence called the hypothalamic attack area (HAA). This HAA consist of an area extending between the caudomedial LH and ventrolateral VMH rostrally alongside the anterior hypothalamic nucleus (see Ref. [38] for detailed review). Electrical stimulation of parts of the HAA induces fierce bite-, lunge-, and kick-attacks in a variety of animals (*e.g.*, rats, cats, monkeys). This hypothalamic-induced attack behavior can be directed against males, females, anesthetized or even dead rats, and is aimed toward vulnerable body parts. It fails to elicit the range of normal introductory/threatening displays and hence this form of electric current-induced attack is clearly representing abnormal or violent-like aggressive characteristics.

However, despite its anatomical precision, stimulation and lesion electrodes still affect a rather ill-defined population of neurons and fibers of passage that do not allow definite conclusions on the precise neuronal and circuit-level mechanisms underlying offensive attack. Newly emerging techniques for mapping, measuring, and manipulating neural activity based on genetic targeting of specific neuron subtypes has solved many of these problems. In particular, optogenetics and related chemicogenetics have made it possible to rapidly and reversibly activate or inhibit small molecularly distinct populations of neurons (anatomical and genetic precision) at any moment in time (temporal precision) [39•,40•] These revolutionary techniques offer the ability to selectively manipulate individual neural circuit elements that underlie aggression-relevant behaviors.

The first experiments investigating the role of the hypothalamus in the regulation of aggression using these newly emerged techniques focused on the ventrolateral subdivision of the VMH (VMHvl). Following virally-delivered expression of the light-sensitive protein channelrhodopsin-2 (ChR2) in this VMHvl region of mice, light pulses delivered through an implanted optic fiber produced robust offensive attacks directed toward males, castrated males, females and even inanimate objects [41•]. On the other hand, inhibiting these neurons using virally expressed *C elegans* ivermectin-gated chloride channel, which prevents the initiation of action potentials by hyperpolarizing the neurons upon ligand (ivermectine) binding (*i.e.*, a chemicogenetic approach), suppressed normal attacks. Recent evidence also established that these VMHvl neurons could mediate not only acute overt attack (consummatory phase of aggression) but also the flexible seeking actions (appetitive phase) that precede biting attacks [42].

Further studies have capitalized on the fact that the neurons of the VMHvl are primarily (>90%) glutaminergic and are enriched with estrogen (Er_α) and/or progesterone (PR) receptors. Both Er_α-knockout mice and RNAi knockdown of Er_α in the VMHvl resulted in a dramatic decrease of natural inter-male aggression [43]. Similarly, ablation of PR-expressing VMH neurons (that overlap with the Er_α–expressing neurons) strikingly reduced aggressive attack [44]. Most recently, optogenetic stimulation of specifically Er_α VMHvl neurons triggered attack behavior while optogenetic silencing suppressed fighting, suggesting that Er_α-endowed neurons in this small hypothalamic area are necessary and sufficient to initiate and terminate attack bouts [45•]. Besides Er_α and PR, these neurons in the VMHvl also express a variety of other neuromodulator receptors, including 5-HT, DA, and OXT receptors. Because many of these neuromodulators change their levels dynamically during the course of aggressive behaviors, they may influence VMHvl neuron excitability and hence aggressive attack.

Similar opto/chemicogenetic interrogations are continuing to be performed in molecularly defined neurons in various other nodes of the well-mapped brain aggression circuitry, that is, glutaminergic, GABAergic and/or aromatase-expressing neurons in the medial amygdala [46,47], glutaminergic neurons in the medial prefrontal cortex [4], GABAergic neurons in the septal nucleus [48],

Galanin neurons in the medial preoptic area [49], and the dopaminergic neurons in the Ventral Tegmental Area [50]. The current type of work certainly will illuminate how the activity of distinct sets of neurons within the various nodes of the basic social behavior neural circuitry give rise to different phases (initiation, execution and termination), levels and/or forms (normal and abnormal) of aggressive behavior.

Synthesis and outlook

A large body of animal neurobehavioral research convincingly demonstrates that abnormal expressions of aggressive behavior principally find its origin in a dysregulation of the deeply rooted neuronal circuits and/or neurochemical pathways in the brain that mediate normal social affiliative-aggressive behaviors. The structural and functional properties of this social behavior brain network are established and constantly shaped by a dynamic interplay of genetic and environmental factors (stress, maltreatment, vicarious experiences, *etc.*) in particular during certain sensitive (*i.e.*, perinatal and adolescent) developmental periods. Undisputedly, among the neurochemical systems that are considered key signaling molecules in this neurocircuitry controlling aggression are the canonical monoamines serotonin and dopamine, the 'social' neuropeptides oxytocin and vasopressin, the 'stress' neuropeptide CRF, the 'stress' HPA- and 'sex' HPG-axis's steroid hormones (corticosterone, testosterone, estrogen), and their receptors. Particularly, from the viewpoint of targeting novel molecular sites for intervention, the intrinsic 5-HT autoregulatory mechanisms (*i.e.*, the presynaptic 5-$HT_{1A/B}$ autoreceptors and 5-HT reuptake transporter), and extrinsic aminergic (DA), neuropeptidergic (*i.e.*, OXT, AVP and CRF) and steroid receptor (*i.e.*, MR and AR) modulatory influences on 5-HT signaling are emerging as important molecular determinants of escalated aggression regulation. This circuit-level knowledge of the neuromolecular underpinnings of escalated aggression has great potential to guide the rational development of effective therapeutic interventions for pathological social and aggressive behavior in humans.

Conflict of interest statement

Nothing declared.

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