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Review

# Escalated aggressive behavior: Dopamine, serotonin and GABA

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**Abstract**

The ethical dilemma in aggression research is how to reconcile two divergent objectives, namely to avoid harm and injury as much as possible and, at the same time, how to study behavioral phenomena that validly represent the essence of the neurobiology of aggression. Clinical and preclinical aggression research focuses on different types of aggression. Preclinical studies are usually stimulated by an ethological approach and focus on the phylogeny, ontogeny, survival value and neural mechanisms of ritualized displays and signals. On the other hand, clinical studies focus on violent individuals and pathologically excessive forms of aggressive behavior.

This review emphasizes research on escalated forms of aggression in animals and humans and their pharmacotherapy. The current experimental models to generate escalated levels of aggressive behavior in laboratory rely on social instigation, frustrative non-reward and alcohol drinking. These types of aggression are modulated by canonical neurotransmitters like dopamine, serotonin (5-HT) and GABA. It continues to be a main goal of much neurobiological research to find potential targets of pharmacological agents that interact with dopaminergic, GABAergic and serotonergic systems and have high efficacy and selectivity to reduce excessive levels of aggressive and violent behaviors without side-effects. While the mesocorticolimbic dopamine system is implicated in the initiation, execution, termination and consequences of aggressive behavior, drugs with a high affinity for dopamine D2 receptors lack specificity for reducing aggressive behavior. Current investigations point to $5\text{-HT}_{1B}$ receptor subtypes as particularly relevant. First, they are differentially expressed in aggression-prone individuals relative to those who are not excessively aggressive. Second, these and also other 5-HT receptor subtypes emerge to be significant targets for anti-aggressive interventions. Positive modulators of $GABA_A$ receptors with specific subunit configuration may be relevant for heightening aggression, and these sites may be targets for intervention. A prerequisite for rational pharmacotherapies will be adequate characterization of serotonergic and GABAergic receptor regulation in individuals exhibiting escalated aggression.


*Keywords:* Aggression; Serotonin; Defense; Frustration; Alcohol; Dopamine; GABA; Neuroleptics; Benzodiazepines

**Contents**



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## 1. Definitions and ethics

In most general terms, aggressive behavior can be considered as a behavior that inflicts harm and injury or threatens to do so (Berkowitz, 1983). One important class of aggressive behavior is characterized by its instrumentality, typically in a reproductive context; males achieve dominance in a social setting by engaging in aggressive displays; in other animal species, males patrol and defend territories in order to secure the resources that attract breeding partners, while females suppress the reproductive functions of rivals and protect and defend their own offspring by engaging in aggressive behavior (Brain, 1981; Huntingford and Turner, 1988). From a biological perspective aggression is important for survival of the individual. In humans, aggression becomes a serious problem when it damages, hurts and injures others, and it is exactly the harm and injury or, at least, the threat thereof, that defines the essence of aggressive behavior. Aggressive outbursts that result in harm and injury are a substantial problem for the public health and criminal justice systems, and this problem is aggravated by the fact that there are no adequate treatment options (Volavka, 1995). The ethical dilemma of aggression research is to reconcile two opposing objectives, namely to avoid harm and injury as much as possible and, at the same time, to study behavioral phenomena that validly represent the essence of the biology of aggression (Miczek, 2001).

One of the challenges for experimental research on aggressive behavior under laboratory conditions is to generate biologically relevant conditions in order to model escalated levels of aggression, as these are the key concerns for the public health and criminal justice systems. These escalated forms of aggression may be considered pathologies in need of control and treatment (Miczek et al., 2004). The main objective of this paper is to review how escalated levels of aggression have been studied in preclinical and clinical settings and to highlight promising pharmacotherapeutic approaches that have been used in the management of aggressive behavior.

## 2. Approaches to study aggression

It is ethically not acceptable to recreate clinically relevant types of aggressive behavior in the experimental human laboratory in real time. Most studies use simulations of symbolic and moderate forms of aggression towards a fictitious competitor (Cherek and Steinberg, 1987), neuroimaging of individuals who have displayed in the past high levels of aggressive behavior (Soloff et al., 2005; George et al., 2004). Alternatively, individuals with a criminal history or in drug abusers are studied (Hoaken and Stewart, 2003; Moeller and Dougherty, 2001). A notable example is the Point Subtraction Aggression Procedure™, developed by Cherek (1981) which allows the quantitative measurement of aggressive responses in real time in response to being repeatedly and unpredictably provoked. In a task with monetary rewards, the experimental subject has the opportunity to retaliate in response to being provoked by occasional losses and then proceeds to subtract some earnings from a fictitious opponent. This procedure has been validated by demonstrating significantly increased aggressive responses by violent parolees (Cherek and Lane, 1999; Cherek et al., 1997b) and showing their sensitivity to the aggression—heightening and—suppressing effects of various psychoactive drugs.

In addition to behavioral studies of aggression under controlled laboratory conditions, further information originates from the use of questionnaires such as

(1) The Aggressive Acts Questionnaire (AAQ) which relies on self-report with 22 items (Barratt et al., 1997);
(2) The revised Buss Durkee Hostility Inventory with four scales including verbal aggression, physical aggression, anger and hostility (Buss and Perry, 1992);
(3) The State-Trait Anger Expression Inventory (STAXI) which measures anger and anxiety (Spielberger, 1983);
(4) The Beck Anxiety Inventory and Back Depression Inventory (Beck et al., 1961) which includes an assessment of aggression;
(5) The Minnesota Multiphasic Personality Inventory (MMPI) which includes measures of impulsivity and hostility (Mckinley et al., 1948); and
(6) The Lifetime History of Aggression (LHA) scale which relies on self-report in 9 behavioral categories ranging from fighting to disciplinary problems (Brown et al., 1979).

While data from scales, inventories, questionnaires and self-reports are important, it is fundamental to obtain behavioral and neurobiological data such as those related to the assessment of neurotransmitters and receptors involved in aggressive behavior.

Neurochemical evaluations of transmitter substances have often relied on assays of samples from the blood and cerebrospinal fluid (CSF), obtained at one time point, and these data were correlated with aggressive and violent behavior, displayed at an earlier time (Brown et al., 1979; Placidi et al., 2001; Virkkunen et al., 1989). This research tactic assumes that the biochemical assay data reflect a stable trait that characterizes an individual (Coccaro et al., 1991). For example, a low “serotonin

trait" in humans has been postulated to be a critical characteristic of the predisposition to engage in impulsive, self-destructive violence but not for instrumental aggression aimed at dominance or reproductive success (Mann, 1999). Similarly, a relationship has also been suggested between aggression and elevated catecholaminergic activity via a COMT polymorphism (Volavka et al., 2004). Violent offenders that undergo pretrial forensic psychiatric investigation and show interpersonal and behavioral features of psychopathy, measured by the revised Psychopathy Checklist (PCL-R), were predicted by significantly low CSF concentrations of 5-HIAA (5-Hydroxyindolacetic acid; Soderstrom et al., 2001). While there is in fact a correlational association between low 5-HIAA levels and psychiatric disorders, this does not necessarily support any causal relationship between low 5-HIAA levels and impulsive aggression or criminality (Balaban et al., 1996). Clinical and preclinical studies investigating the link between serotonin activity and aggression seem to be still awaiting a cogent demonstration of cause–effect relationships. In particular, human serotonergic activity can be in some cases related to aggressive behaviors but several investigations suggest that social factors seem to strongly modulate this link (Badawy, 1999). Serotonergic dysfunction such as altered levels of brain 5-HT influence aggression differently in humans, depending on the individual's impulse control, emotional regulation, and social abilities (Badawy, 1999). Serotonergic function has an effect not only on the individual but also on the group dynamics, and it is in turn influenced by these dynamics. Whether aggression will occur when a serotonin dysfunction is evident will depend on individual differences as well as on the overall social context (Krakowski, 2003).

Finding potential targets of pharmacological agents continues to be the main objective of much neurobiological research (Sellers et al., 1997). Drugs that act as agonists or antagonists at dopaminergic, GABAergic and serotonergic receptors or as inhibitors of the transporter molecules for uptake of monoamines continue to be used for the pharmacotherapy of violent individuals (Netter, 2001; Brady et al., 1998; Rodriguez-Arias et al., 1998).

Clinical and preclinical aggression research focuses on different types of aggression. Preclinical studies are usually stimulated by an ethological approach and focus on the phylogeny, ontogeny, survival value and neural mechanisms of ritualized displays and signals (Tinbergen, 1968). By contrast, clinical studies focus on violent individuals and pathologically excessive forms of aggressive behavior.

## 3. Preclinical aggression research

Early laboratory studies of animal aggression began by inducing intense aggressive and defensive reactions in otherwise placid laboratory animals by brain lesions or electrical brain stimulation, by provoking animals with noxious painful stimuli or housing them in isolation for prolonged periods, or by exposing them to frustrating experiences (e.g., Valzelli, 1973; Yen et al., 1959; Ulrich, 1966; Ulrich and Azrin, 1962; Azrin et al., 1966; Hess and Brugger, 1943; Koolhaas, 1978; Brady and Nauta, 1953). These experimental approaches were re-evaluated and replaced by ethologically inspired studies of aggressive behavior in various animal species (Lorenz, 1966; Eibl-Eibesfeldt, 1970). An initial step in the ethological study is the accurate description and analysis of aggressive behavior (i.e. ethogram) in socially organized and cohesive animal species, such as in most primates and rodents, where the establishment and maintenance of a social hierarchy is achieved by aggressive displays, acts and postures. In addition to this type of dominance aggression, several commonly used laboratory animals such as mice (*Mus musculus*) display social behavior that is governed by dispersive rather than cohesive forces (Crowcroft and Rowe, 1963). Aggression by these rodents is usually referred to as territorial because rivals are excluded from a territory rather than tolerated. These forms of aggression are typically displayed by males while competing for resources and mates. Females may also become aggressive, usually in the postpartum period, in order to defend their young (Svare and Gandelman, 1973; Mackintosh, 1981; Erskine et al., 1978; Mos and Olivier, 1986; Lucion and de Almeida, 1996; Palanza et al., 2005).

Aggression can be considered an adaptive behavior when it serves a specific function such as for example, in a reproductive context, or by securing access to food, secure and safe sleeping places or by protecting the young. The classic ethological approach aims to trace the ontogenetic and phylogenetic origins of aggressive behavior, to assess the survival function of this behavior for the species and its causation (Tinbergen, 1951). It is useful to consider some characteristics of male and female aggressive behavior, and compare these species-normative types behavior patterns with escalated forms.

### 3.1. Dominance behavior

Rats are one species which lives socially and form "dominance territory" (Barnett, 1975, 2005). Like in primates, the aggressive behavior is most frequent during the formation of a dominance hierarchy (macaques (Bernstein and Gordon, 1974), rats (Steiniger, 1950)). The behavioral repertoire of dominance aggression comprises acts, postures, and displays that develop during play fighting in the pre-pubertal period (Pellis and Pellis, 1987). From a sociobiological perspective, the primary function of dominance aggression may be to secure resources for successful transmission of genetic information into the next generation, and the ritualization of aggressive displays reduces the probability of injury (Silk et al., 2003).

### 3.2. Territorial aggression

The primary function of territorial aggression is to disperse breeding individuals, starting after puberty (van Oortmerssen and Bakker, 1981). For example, this type of behavior can be observed in tree shrews (*Tupaia belangeri*) and in mice (*M. musculus*); they mark, patrol and guard their territory (Von Holst, 1969; Crawley et al., 1975), and all intruders are forcefully confronted. To be excluded from the guarded and marked territory represents an example of "exclusive territory," whereas to be dominated within the boundaries of an existing territory is

referred to as "dominance territory" (Eibl-Eibesfeldt, 1950). In aggression research with laboratory mice, territorial aggression is the basis for the common experimental protocol in which a breeding resident male confronts an intruder (Miczek and O'Donnell, 1978; Crawley et al., 1975).

### 3.3. Female aggression

One purpose of female aggression is to defend the offspring. In a broader sense, the function of female aggression is to suppress the reproductive success of rival females and further the survival of the female's own offspring (Hurst, 1987). Lactating female mice and rats engage in aggressive behavior similar to males, they attack intruding males and females when the litter is present. The female lunges toward and bite their opponent's snout and head, often including jump attacks (Sgoifo et al., 1992; Lucion and de Almeida, 1996). Non-lactating females engage in aggressive behavior toward female rivals, and this type of aggression shares many behavioral characteristics with that of males.

## 4. Types of escalated aggression

In social species, the aggressive behavior can serve an important adaptive function. Nevertheless, when this type of behavior exceeds the species-typical pattern, it becomes maladaptive. Escalated or excessive levels of aggressive behavior can be induced in laboratory animals or humans by (a) pharmacological (alcohol-heightened aggression), (b) environmental (social instigation), (c) behavioral (frustration-induced aggression) means or (d) by genetic selection (de Boer and Koolhaas, 2005—this issue). It is instructive to study these forms of escalated aggressive behavior in order to investigate the neurochemical mechanisms involved in aggression and violence that are in need of treatment (Miczek et al., 2002).

### 4.1. Alcohol-heightened aggression

Alcohol more than any other drug is involved in many types of aggressive behavior (Chermack and Giancola, 1997; Brown et al., 1999; Fulwiler et al., 2005)in more than 50% of all violent crimes (Murdoch et al., 1990) and up to 86% of murders (Roizen, 1997). Alcohol-heightened aggression is expressed towards others who are also alcohol-intoxicated or not, and it ranges from murders, homicides, sexual assaults to domestic violence (Trezza and Popp, 2000). Human correlative statistics show that most people who drink do not become aggressive after consumption of alcohol under controlled laboratory conditions (Lang et al., 1975). It has been suggested that aggression-related personality traits may mediate individual responses to alcohol (Bjork et al., 2004; Mazas et al., 2000; Moeller et al., 1998; Cherek et al., 1992).

It is interesting to note that alcohol can decrease aggression in many animal species such as in mice, rats, monkeys and in humans, presumably due to the sedative effects (Krsiak and Borgesova, 1973; Smoothy and Berry, 1983). At low to moderate doses, alcohol increases significantly aggression in certain individuals (Fig. 1); and these individual differences in alcohol effects on aggression are the focus of several investigations (Miczek and Barry, 1977; Peeke and Figler, 1981; Cherek et al., 1984; Blanchard et al., 1987; Miczek et al., 1992, 1994; Berry, 1993; Van Erp and Miczek, 1997; de Almeida et al., 2001b; Miczek and de Almeida, 2001; de Almeida and Miczek, 2002; Faccidomo et al., submitted for publication). Laboratory studies in rats and mice have shown that only a subgroup of individuals (ca. 20–30%) becomes consistently highly aggressive while under the influence of moderate amounts of alcohol (Miczek et al., 1992, 1998a,b; Miczek and de Almeida, 2001; Van Erp and Miczek, 1997; Fish et al., 1999; Faccidomo et al., submitted for publication).

### 4.2. Social instigation

In 1971, Cherek and Heistad used an experimental manipulation where the subjects were provoked by having points subtracted which are earned in a competitive task (Cherek and Heistad, 1971). The point losses were attributed to a fictitious opponent, but determined by a computer program according to a random schedule. The subjects responded by retaliation of point subtractions, then the aggression responses were the number of point subtractions from a fictitious competitor. This experimental protocol was successfully replicated in control individuals, parolees of violent crimes, poly-drug users, female subjects (Bjork et al., 1996; Giancola and Chermack, 1998; Cherek et al., 1997a,b). For example, several studies showed that alcohol and benzodiazepines increase aggression in moderate doses (Cherek et al., 1985; Bjork and Dougherty, 1998; Weisman et al., 1998).

An experimental protocol for social instigation in laboratory rats and mice was developed that captures the intense escalation of aggressive behavior that results from the exposure to an

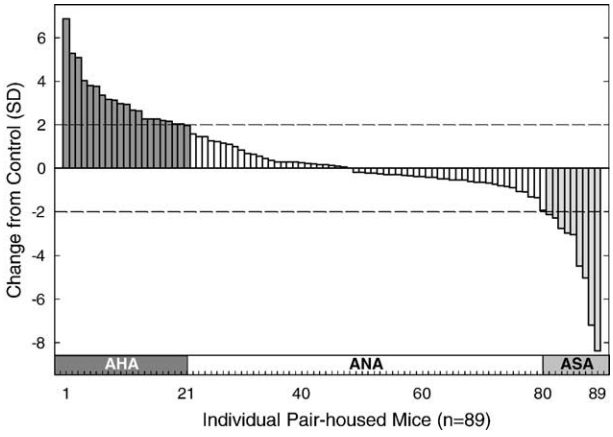


Fig. 1. Effects of a 1.0 g/kg p.o. ethanol challenge on attack bite frequency toward a male intruder by individual pair-housed male mice. Each bar depicts the standardized data for one resident mouse, ordered according to the magnitude of the change due to ethanol treatment relative to the individual's vehicle control level. The change is expressed in standard deviations, and the dotted horizontal lines show the ±2 S.D. cutoffs that were used to identify individuals exhibiting alcohol-heightened aggression (AHA) or alcohol-suppressed aggression (ASA) versus those who did not show a significant change (alcohol-nonheightened aggression, ANA). From (Miczek et al., 1998a).

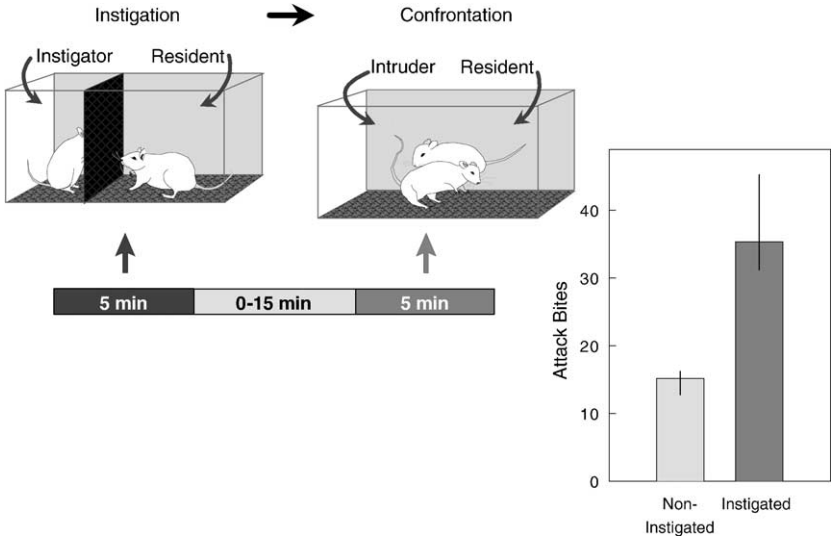


Fig. 2. Effects of social instigation on aggressive behavior by a resident mouse toward a male intruder. The resident mouse is exposed to another male behind a protective screen for 5 min; after a specific interval, the resident is then confronted by an intruder. Bars represent the frequency (medians, IQR) of attack bites under control (light grey) and instigated (dark grey) conditions. From (Miczek et al., 2004).

opponent for a short time behind a protective screen prior to the actual confrontation (Potegal, 1991). This procedure is referred to as "attack priming" or social instigation. In general, hamsters, mice and rats initiate attacks with very short latency and at high frequency when tested with an intruder in their home cage or in an unfamiliar environment after having been provoked previously by the presence of an opponent (Potegal, 1991; Fish et al., 1999; de Almeida and Miczek, 2002). (Fig. 2) Social instigation specifically increases aggression, and does not activate other activities such as feeding, sexual behavior or locomotion (Lagerspetz and Hautojarvi, 1967; Potegal and Tenbrink, 1984; Potegal, 1991). Very high levels of aggression are observed toward the "instigator" or another opponent, presumably due to increased "aggressive arousal" or "attack readiness."

### 4.3. Frustration

Human experimental data have been collected by experimental manipulations to count the aggressive responses toward a competitor, using electric shock settings on a scale from 1 to 10, each corresponding to a different intensity or duration of electric shock, has been measured in control individuals, criminal offenders and drug users (Buss, 1961; Taylor, 1967). Recent replications of this research protocol were performed under varied conditions to assess aggression and involved various drug treatments (Scheier et al., 1974; Bernstein et al., 1987; Gustafson, 1992; Giancola and Chermack, 1998). Using this and similar protocols, moderate doses of alcohol, cocaine, morphine and delta$^9$-Tetrahydrocannabinol increase aggression (Bennett et al., 1969; Moeller et al., 2001; Licata et al., 1993; Berman and Taylor, 1995; Taylor et al., 1976; Lau and Pihl, 1994).

In human experimental studies procedures are implemented in order to assess how well an individual tolerates delay of gratification. One important factor that has been hypothesized to lead to frustrative experiences that manifest themselves in aggressive and violent outbursts is the inability to tolerate delayed gratification (Dollard et al., 1939). A low frustration threshold is characteristic of violent youths (Nock and Kazdin, 2002; Calkins and Johnson, 1998; Matthews and Norris, 2002). Surprisingly, little is known about the neural mechanisms that are responsible for increased vulnerability or, alternatively, resilience to engage in frustration-induced aggression. It will be essential to learn how such aggressive outbursts are linked to specific neural activity as well as what receptors exert a crucial role in this kind of behavior.

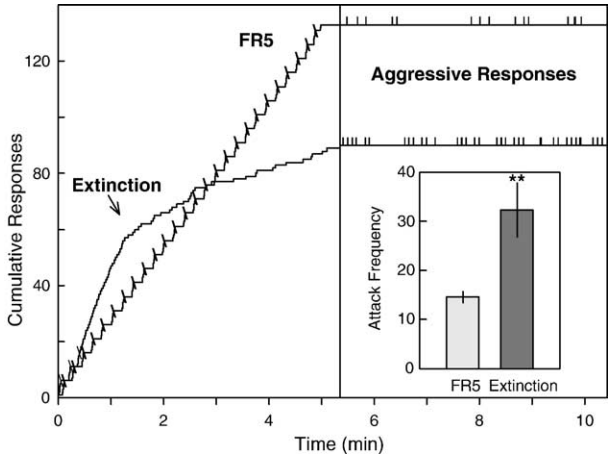


Fig. 3. Heightened aggression after exposure to the sudden omission of scheduled reinforcement of responding ("frustration-induced" aggression). Left: Cumulative responses under the control of a fixed ratio 5 schedule of reinforcement, with each reinforced response denoted by a slash. In the extinction condition, reinforcement is stopped after the third delivery. Right: Time line with vertical deflections indicating the resident mouse's aggressive responses when an intruder mouse is presented at the end of the conditioning session. Inset: The frequency of attack bites (mean ± S.E.M.) in nonextinction (light grey bar) and extinction (dark grey bar) tests. Two asterisks depict $P<.01$. From (Miczek et al., 2002) ©2002 Springer-Verlag.

Bursts of aggression can be displayed after discontinuation of scheduled reinforcements in many different non-human species including pigeons, rats, mice and monkeys (Fig. 3) (Amsel and Roussel, 1952; Azrin et al., 1966; Thompson and Bloom, 1966; Cherek and Pickens, 1970; Kelly, 1974; Caprara, 1982; Evenden and Ryan, 1996; de Almeida and Miczek, 2002).

## 5. Escalated forms of aggression and neurotransmitters

The role of neurotransmitters and their receptors and transport sites in preclinical studies of aggression has guided much of the development of pharmacotherapeutic interventions during the past decades (Miczek et al., 2002). The focus on the canonical aminergic transmitters such as dopamine, norepinephrine and serotonin, while still the basis for current drug treatments of violent individuals, has been complemented by a better understanding of modulatory influences by glutamate and GABA as well as neuropeptides and neurosteroids. These amino acid neurotransmitters and neuromodulators promise to offer novel targets for clinical treatment of violent individuals (Miczek et al., 2004; Miczek and Fish, 2006). In early preclinical research, the inhibitory action of serotonin and GABA on aggressive behavior was highlighted, based primarily on post-mortem tissue assays (Mandel et al., 1979; Simler et al., 1983). In the meantime, knowledge of different receptor subtypes and transporter molecules for serotonin, dopamine, GABA and glutamate prompts a replacement of the simple functional label of inhibition or facilitation of aggression that is attached to a particular transmitter. For example, the 5-$HT_{1A}$ and 5-$HT_{1B}$ receptors exert functionally opposing roles in various behavioral and physiological activities such as appetite, sexual libido, motor activity, and it is feasible to extrapolate this divergence to aggressive behavior (Jenck et al., 1989; Dulawa et al., 2000; Olivier, 2004; Faccidomo et al., 2005).

### 5.1. Dopamine

In human aggression, the most frequent and enduring pharmacotherapeutic interventions rely on compounds that act as dopaminergic antagonists (McDougle et al., 1998; Gualtieri and Schroeder, 1990; Yudofsky et al., 1984). For example, the dopamine $D_2$ receptor antagonist haloperidol has been used for decades to treat aggressive behavior in patients who are psychotic (Fitzgerald, 1999; Glazer and Dickson, 1998). This drug also decreases violent outbursts in individuals with dementia and individuals with borderline personality disorder as well as in children and adolescents, who exhibit conduct-disorder and aggression (Masi, 2004; Diederich et al., 2003; Kennedy et al., 2001; Challman and Lipsky, 2000; Beauchaine et al., 2000; Pies and Popli, 1995). The decrease in aggression is closely linked to the sedative effects of haloperidol which renders this therapeutic option as less than ideal.

In preclinical studies the role of dopamine $D_1$, $D_2$ and $D_3$ receptors in the modulation of aggression has been documented (Miczek et al., 2004, 2002; Sanchez et al., 1993; Tidey and Miczek, 1992a,b). Clozapine and (−)-octoclothepin (compounds with multiple actions at dopamine, 5-$HT_2$ receptor and alpha1-adrenoceptor antagonist) show antiaggressive effects. SCH 23390 (dopamine $D_1$ receptor antagonist) and emonapride (dopamine $D_2$ receptor antagonist) reduce aggression in isolated male mice (Sanchez et al., 1993) revealing no differentiation between these two families of receptor subtypes.

More persuasive evidence for a significant role of dopamine $D_2$ receptors stems from studies that focus on defensive-aggressive behavior in cats. Dopamine $D_2$ receptors in the region of the medial preoptic area and anterior hypothalamus facilitate affective defense behavior in the cat. Microinjection of the dopamine $D_1$ antagonist SCH 23390 into this region did not inhibit apomorphine-induced facilitation of hissing in cats, but the injection of haloperidol and sulpiride did inhibit this affective defensive behavior. These results suggest that dopaminergic stimulation of the dopamine $D_2$ receptors in the mPOA-AHA region facilitate the expression of affective defense behavior in the cat (Sweidan et al., 1991).

It is still questionable whether the strategy of the past decades to target mesocorticolimbic dopamine and particularly the dopamine D2 receptor subtype for anti-aggressive effects is most relevant. Several studies indicate that the mesocorticolimbic dopamine system is involved in the preparation, execution and consequences of aggressive acts (Van Erp and Miczek, 2000; Ferrari et al., 2003; Haney et al., 1990; Mos and Van Valkenburg, 1979; Puglisi-Allegra and Cabib, 1990; Louilot et al., 1986). These neurochemical studies link elevated dopamine and its metabolites in prefrontal cortex and nucleus accumbens not only to the initiation of attacks and threats and its consequences, but also to the defensive and submissive responses in reaction to being attacked (Puglisi-Allegra and Cabib, 1990; Tidey and Miczek, 1996). This lack of differentiation in mesocorticolimbic dopamine activity between attack and defensive behavior suggests that neuroleptic compounds with a high affinity for dopamine $D_2$ receptors would not be specific anti-aggressive treatments.

Pharmacologically induced dopamine increases are associated with increased aggressive behavior under some conditions. Low to moderate doses of amphetamine or apomorphine can heighten aggression of isolated mice or rats after omission of a scheduled reward, often referred to as frustrative non-reward. Higher doses of amphetamine also increase the defensive responses of rats reacting to electric shock or to the attacks by an opponent—these are examples of behavioral changes which are likely to be due to altered general stimulus reactivity or arousal, similar to the earlier discussed evidence from hypothalamically stimulated cats (Senault, 1968, 1971; Crowley, 1972; Hasselager et al., 1972; Miczek, 1974; Puech et al., 1974; Ray et al., 1983). When undergoing withdrawal from morphine, a state with profound neurochemical sequelae including suppressed dopaminergic activity (Diana et al., 1995; Nowycky et al., 1978), amphetamines enhance aggression in mice and rats (Gianutsos and Lal, 1978; Kantak and Miczek, 1988; Tidey and Miczek, 1992b). Amphetamines can also increase aggressive behavior indirectly, by preventing fatigue, particularly during extended fights (Winslow and Miczek, 1983). However, these agents frequently disrupt both aggressive and social

behavior in animals with a prior history of extensive aggressive experiences (Hodge and Butcher, 1975; Miczek and O'Donnell, 1978; Miczek and Yoshimura, 1982; Miczek and Haney, 1994).

Two major enzymes are responsible for catecholamine catabolism in the brain: catechol-*O*-methyltransferase (COMT) and monoamine oxidase A (MAO-A). If aggressive behavior is enhanced by catecholaminergic activity, then the lower activity of COMT and MAO-A (resulting in a slower inactivation of catecholamines) should indirectly enhance aggression. This prediction has been supported by most, but not all observations in rodents and humans. Male mice that have either the COMT or the MAO-A gene deleted show elevated aggression (Gogos et al., 1998; Cases et al., 1995) implicating these enzymes in the inhibition of aggressive behavior in placid laboratory mice. Several studies implicate a biallelic single nucleotide polymorphism of COMT, with methionine substituting for valine, with increased violent behavior, in a small subgroup of schizophrenic patients (reviewed by (Volavka et al., 2004). Both the mouse knock-out data and the human polymorphism of low COMT activity point to a risk for increased aggressive behavior preferentially in males. In patients with milder types of aggressive behavior and with suicidal tendencies, no or very weak associations with the methionine allele were observed. While intriguing, these observations highlight the limitations of the monogenetic approach to complex behavior patterns such as aggressive outbursts in mental disordered male patients.

The evidence from MAO-A knock-out mice and polymorphisms in humans constitutes probably the most significant contribution to our understanding of gene–environment interactions and their relevance to aggressive behavior (Ferrari et al., 2005—this issue). The data from the mutant mice with specific deletion of the gene for MAO-A point to increased aggressive behavior as one of the salient sequelae of this mutation (Cases et al., 1995). Human data from eight males in an extended Dutch family with a rare sex-specific point mutation in the MAO-A gene provided earlier support for a role of this gene in the likelihood for impulsive aggressive behavior (Brunner et al., 1993). As discussed recently (Ferrari et al., 2005—this issue), MAO-A polymorphism is related to aggressive behavior via salient experiences in early development in the form of maltreatment (Caspi et al., 2002). Only individuals with high levels of MAO-A transcriptional activity were less likely to display a disposition toward violence and other antisocial behavior when maltreated relative to those individuals with low levels of MAO-A transcriptional activity. These MAO-A polymorphism effects are not only relevant to the role of brain DA activity in aggressive behavior, but to other monoamines, most prominently serotonin.

### 5.2. Serotonin

The long postulated important inhibitory role of brain serotonin is difficult to reconcile with the molecular diversity of the serotonergic mechanisms of action (Ferrari et al., 2005—this issue). The identification of genes for at least 14 receptor proteins, variants of the synthetic and metabolic enzymes and transporter molecules demands a careful analysis of the functional significance of this molecular multitude.

Traditionally, many studies have shown that elevated serotonin levels lead to decreased aggression in many different species (Chiavegatto and Nelson, 2003), including humans (Coccaro et al., 1994; Unis et al., 1997). This finding has been replicated in populations of impulsive offenders, adults and children (Brown et al., 1979; Linnoila et al., 1983). However, some studies have not detected this inverse relationship between the propensity to engage in aggressive behavior and a deficiency in serotonin neurons (Yodyingyuad et al., 1985; Volavka et al., 1990; Van Der Vegt et al., 2003).

Preclinical experiments have provided evidence for a significant role of 5-$HT_1$ and 5-$HT_2$ receptor families in aggression (Olivier et al., 1989; Olivier and Mos, 1992; Barrett and Vanover, 1993; de Almeida and Lucion, 1997, 1994; de Almeida et al., in press). Activation of the 5-$HT_{1A}$ receptors has been shown to decrease aggression, after administration either systemically or directly into the brain. The most significant side-effect of 5-$HT_{1A}$ receptor agonists pertains to its action on motor functions, as evident by slowing movements and increasing repetitive routines in many individuals (de Almeida and Lucion, 1997; Sanchez and Meier, 1997; Miczek et al., 1998b).

The 5-$HT_{1B}$ receptors are of potential importance as target for treatment of disorders such as depression, schizophrenia, Parkinson's disease, and impulsive disorders (Boulenguez et al., 1998; Moret and Briley, 2000; Audinot et al., 2001; Millan et al., 2002). Drugs acting as agonists at 5-$HT_{1B}$ receptors, however, when administered systemically, potently and efficaciously inhibit several types of aggressive behavior in mice (Fish et al., 1999) for review see (Miczek et al., 2002). Systemically administered 5-$HT_{1B}$ receptor agonists such as CP-94,253, anpirtoline and zolmitriptan exert anti-aggressive effects in mice with moderate as well as high levels of aggression without impairing non-aggressive activities (Fig. 4) (Fish et al., 1999; de Almeida et al., 2001b, in press; de Almeida and Miczek, 2002). Further support for the significant role of this receptor subtype derives from the finding of increased aggression in mutant 129Sv mice lacking the 5-$HT_{1B}$ receptor gene (Saudou et al., 1994; Bouwknecht et al., 2001).

Activation of pre-synaptic 5-$HT_{1B}$ receptors inhibits 5-HT release and decreases extracellular concentrations of 5-HT in the cortex, ventral hippocampus, striatum, and diencephalon (Engel et al., 1986; Hoyer and Middlemiss, 1989; Hjörth and Sharp, 1991; Chopin et al., 1994; Martin and Humphrey, 1994; Rollema et al., 1996; Roberts et al., 1997; Knobelman et al., 2000) (for review, see Sari, 2004). In vivo microdialysis data confirmed a 30–40% suppression of extracellular 5-HT in mouse prefrontal cortex (PFC) after CP-94,253 administration of an anti-aggressive 10 mg/kg dose, pointing to a possible action of this agonist at presynaptic receptors, in addition to postsynaptic action (Bannai et al., in press).

Recently, the role of important cortical areas in aggression and impulsive behaviors has been studied using microinjections of serotonergic agents into specific regions that are rich in 5-$HT_{1B}$ and 5-$HT_{2A}$ receptor subtypes (Wall et al., 2004; de Almeida et al., in press). Pharmacological activation of

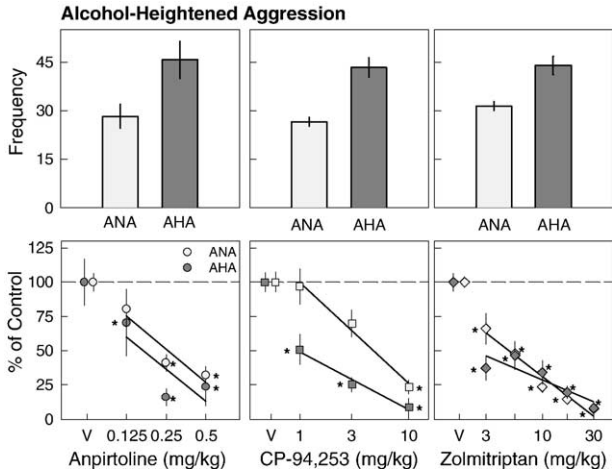


Fig. 4. Top: Certain mice are more aggressive than others following experimenter-administered oral ethanol (center and right panels) or orally self-administered ethanol (1.0 g/kg). Bars represent the mean frequency of attack bites ±SEM (vertical lines) toward an intruder for the subset of mice identified as alcohol-nonheightened aggressors (ANAs, light grey bars) and alcohol-heightened aggressors (AHAs, dark grey bars). Bottom: Reduction of aggressive behavior in ANAs (light grey symbols) and AHAs (dark grey symbols) that were exposed to 1.0 g/kg of ethanol and subsequently treated with the 5-$HT_{1B}$ receptor agonist anpirtoline (left panel, circles), CP-94,253 (center panel, squares), or zolmitriptan (right panel, diamonds). Data are expressed as a percentage of vehicle baseline. Symbols represent the mean number of attack bites ±S.E.M. (vertical lines). Asterisks denote statistical significance relative to vehicle ($P<.05$). From (Miczek et al., 2002); ©2002 Springer-Verlag.

these receptors in the prefrontal cortical area and the periaqueductal area inhibits the execution of aggressive behavior (de Almeida et al., in press). Recently, the prefrontal cortex, more specifically the orbitofrontal region has been identified to be particularly important in the inhibitory control of behavior, mainly impulsive and aggressive behavior (Blair, 2001; Seguin, 2004; Cardinal et al., 2004; Spinella, 2004; Kheramin et al., 2005). However, in alcohol-consuming mice, microinjection of the 5-$HT_{1B}$ receptor agonist CP 94253 into the infralimbic region of the prefrontal cortex actually increases aggressive behavior pointing to postsynaptic sites of action on neurons that are part of a more complex feedback circuit (Faccidomo et al., 2005).

When activated systemically, 5-$HT_{1B}$ receptors appear to be essential sites for the inhibition of several types of aggressive behavior. The decrease of heightened aggression was observed in studies using mice after intraperitoneal administration of 5-$HT_{1B}$ receptor agonists such as CP-94,253, zolmitriptan and anpirtoline (Fish et al., 1999; de Almeida et al., 2001a, 2002) or microinjection of CP-94,253, using mice and rats (de Almeida et al., in press). The most recent studies showed that the prefrontal cortex is one of the principal brain areas related to reducing aggression in rodents.

### 5.3. GABA

Earlier postmortem studies showed that brain levels of GABA and glutamic acid decarboxylase (GAD), in brain areas such as the striatum and the olfactory bulbs are low in mice and rats that exhibited aggressive behavior (Clement et al., 1987; Guillot and Chapouthier, 1998; Haug et al., 1987). These data have been interpreted as concordant with the proposed inhibitory role of GABA on aggression. Further support for this view derived from pharmacological studies. When GABA transaminase is blocked with sodium *n*-dipropylacetate or valproate or when reuptake is inhibited by diaminobutyric acid or nipecotic acid amide, aggressive behavior is inhibited in mice and rats (Puglisi-Allegra et al., 1979; Puglisi-Allegra and Mandel, 1980; Krsiak et al., 1981; Rodgers and Depaulis, 1982). Bjork et al. (2001) found a positive relationship between plasma GABA and aggressiveness as assessed by the Buss–Durkee Hostility Inventory in psychiatrically healthy adults with a family history of psychiatric disorders, although it is unclear how plasma levels are related to those in neural tissue.

Clinical studies show that the benzodiazepines reduce aggressive behavior, in addition to the well-characterized tranquilizing, anti-anxiety, sedative and muscle-relaxing effects, although reports of increased aggressive outbursts persist, ever since the introduction of these compounds nearly five decades ago in hostile outpatients, psychotic patients and patients with episodic dyscontrol (Friedel, 2004; DiMascio, 1973; Cherek and Lane, 2001; Jonas et al., 1992). Benzodiazepines enhance the activity of GABA via their positive modulation of the $GABA_A$ receptor subtype. Psychiatric patients with violent outbursts as well as those with episodic dyscontrol syndrome are treated with these compounds (Friedel, 2004; Gregg and Siegel, 2001; Cherek and Lane, 2001; Jonas et al., 1992). At higher doses, these drugs can cause lack of muscle control and loss of consciousness. Other adverse effects include hypotension, dizziness, confusion, and aggression (Daderman et al., 2003; Slaughter, 2000).

In human experimentation, triazolam dose-dependently decreased in positively and negatively reinforced behavior and

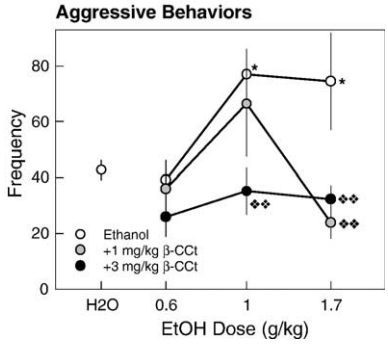


Fig. 5. Frequency of aggressive behaviors (attack bites, sideways threats and pursuits) as a function of self-administered ethanol dose (g/kg) in male resident mice confronting an intruder. The resident mice were previously categorized as alcohol-heightened aggressors (AHA). The measurements were obtained from the AHA mice after they had self-administered various doses of ethanol only and then confronted an intruder (clear circles) or after ethanol self-administration and treatment with 1 mg/kg (i.p.; grey circles) or 3 mg/kg of β-CCt (black circles). For comparison, the level of attack bites and sideways threats after water vehicle self-administration is shown. The asterisks denote significant differences between the values from tests after alcohol self-administration and after water vehicle consumption ($P<0.05$), and diamonds indicate significant differences ($P<0.01$) between the values from alcohol effects in the presence and absence of β-CCt. From (de Almeida et al., 2004); ©2004 Springer-Verlag.

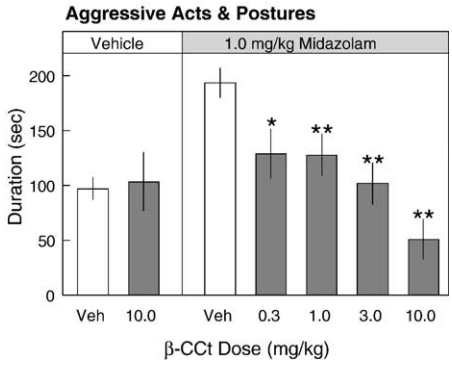


Fig. 6. The effects of β-CCt on the duration of aggressive acts and postures in resident rats confronting an intruder for 5 min. On the left, the effects of β-CCt are shown in vehicle-treated animals, and on the right, in midazolam-treated (1.0 mg/kg) animals. The vertical lines in each bar identify ±1 S.E.M. Asterisks indicate statistically significant differences between a specific drug treatment and the corresponding vehicle control (*$P<0.05$, **$P<0.01$). From (Gourley et al., 2005); ©2004 Springer-Verlag.

also aggressive responding (Cherek et al., 1991). Jonas et al. (1992) compared the efficacy, safety, and performance of triazolam to those of short-acting hypnotics acting on the $GABA_A$ receptor (e.g., zopiclone, zolpidem, midazolam, brotizolam, temazepam, lormetazepam, and loprazolam). Two findings emerged; first, "serious" central nervous system side effects, such as excitement and violence, were not demonstrated for any of the hypnotic agents, including triazolam. Other central nervous system side effects, such as depression and irritability, were reported with equal frequencies for all the benzodiazepine hypnotics.

Positive modulators of the $GABA_A$ receptor complex, such as ethanol, midazolam and allopregnanolone, can effectively increase aggressive behavior in a range of situations and species (see Fig. 1) (Miczek et al., 2003; Fish et al., 2001, 2005). Non-selective benzodiazepine receptor antagonists such as flumazenil effectively prevent the aggression-heightening effects of diazepam and ethanol (Olivier et al., 1991; Miczek et al., 1993).

Zolpidem is a compound that has a greater selectivity for $GABA_A/\alpha_1$ receptors over other $GABA_A$ receptor subtypes (Sanger and Zivkovic, 1986; Damgen and Luddens, 1999). Zolpidem effectively sedates aggressive mice, and does not increase aggressive behavior at low doses as is characteristic for most benzodiazepines such as midazolam, diazepam and chlordiazepoxide (Miczek, 1974; Miczek and O'Donnell, 1980; Rodgers and Waters, 1985; Gourley et al., 2005). In male mice, triazolam and zolpidem decreased alcohol-heightened and non-heightened aggressive behavior, and these antiaggressive effects were accompanied by reduced motor activity, indicating sedation. Benzodiazepine antagonists, particularly those acting preferentially at $GABA_A/\alpha_1$ subunit-containing receptors, decrease midazolam- and alcohol-heightened and species-typical aggressive behavior, but are ineffective in attenuating the sedative effects of alcohol (Figs. 5 and 6) (de Almeida et al., 2004; Gourley et al., 2005).

One of the neurobiological mechanisms for escalated aggressive behavior may involve increased activation of $GABA_A$ receptors that are modulated by the prevailing serotonergic tone in corticolimbic projection areas. There is abundant neurochemical and behavioral evidence that GABA and 5-HT interact in various brain regions. For example, the raphe nuclei receive a large GABAergic input and contain many GABAergic interneurons (Harandi et al., 1987). In the raphe between 70–90% of serotonergic neurons also contain the α1 subunit of the $GABA_A$ receptor (Gao et al., 1993). It will be important to define the molecular basis for the interactions between 5-HT and GABA, as they escalate aggressive behavior.

## 6. Conclusions

From an ethological perspective, the term "violence" is not relevant, since its focus is on adaptive forms of aggressive behavior, which are significant in terms of the individual's survival and reproduction. Animal models of hostile and violent symptoms in psychiatric disorders are necessary in order to be relevant to the study of the neurobiological basis of human violence.

The recent observations point to serotonin receptor subtypes such as the $5\text{-}HT_{1B}$ receptor as particularly important for two purposes. First, aggression-prone individuals express these receptors differentially relative to those individuals who are not excessively aggressive. Second, these and other 5-HT receptor subtypes appear to be important targets for specific anti-aggressive interventions.

The modulation of GABA and $GABA_A$ receptors by 5-HT in corticolimbic neurons promises to be a particularly relevant mechanism for targeting specific forms of escalated aggressive behavior such as alcohol-heightened aggression. A promising hypothesis focuses on specific subunit configurations of the $GABA_A$ receptors as sites for aggression-heightening effects of positive modulators of this receptor subtype and for pharmacotherapeutic intervention.

Information from molecular and behavioral biology has proven to be important to improve the methodological tools for aggression research and to enhance the understanding of the determinants for escalated aggression and violent behaviors and how it will be possible to treat it with efficacy.

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