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# Brain Serotonin Receptors and Transporters: Initiation vs. Termination of Escalated Aggression

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## Abstract

**Rationale—**Recent findings have shown a complexly regulated 5-HT system as it is linked to different kinds of aggression.

**Objective—**We focus on (1) phasic and tonic changes of 5-HT and (2) state and trait of aggression, and emphasize the different receptor subtypes, their role in specific brain regions, feed-back regulation and modulation by other amines, acids and peptides.

**Results—**New pharmacological tools differentiate the first three 5-HT receptor families and their modulation by GABA, glutamate and CRF. Activation of 5-$HT_{1A}$, 5-$HT_{1B}$ and 5-$HT_{2A/2C}$ receptors in mesocorticolimbic areas, *reduce* species-typical and other aggressive behaviors. In contrast, agonists at 5-$HT_{1A}$ and 5-$HT_{1B}$ receptors in the medial prefrontal cortex or septal area can *increase* aggressive behavior under specific conditions. Activation of serotonin transporters reduce mainly pathological aggression. Genetic analyses of aggressive individuals have identified several molecules that affect the 5-HT system directly (e.g., Tph2, 5-$HT_{1B}$, 5-HT transporter, Pet1, MAOA) or indirectly (e.g., Neuropeptide Y, αCaMKII, NOS, BDNF). Dysfunction in genes for MAOA escalates pathological aggression in rodents and humans, particularly in interaction with specific experiences.

**Conclusions—**Feedback to autoreceptors of the 5-$HT_1$ family and modulation via heteroreceptors are important in the expression of aggressive behavior. Tonic increase of the 5-$HT_2$ family expression may cause escalated aggression, whereas the phasic increase of 5-$HT_2$ receptors inhibits aggressive behaviors. Polymorphisms in the genes of 5-HT transporters or rate-limiting synthetic and metabolic enzymes of 5-HT modulate aggression, often requiring interaction with the rearing environment.

### Keywords

aggression; serotonin; GABA; glutamate; CRF; raphe; prefrontal cortex; hypothalamus; septum; gene regulation

## 1. Preamble

Novel findings with tools from molecular genetics and receptor pharmacology in conjunction with more differentiating behavioral and clinical analysis begin to focus on the prominent role of brain serotonin in the predisposition to initiate impulsive aggressive behavior and the termination of bursts of aggressive behavior (Lesch and Merschdorf 2000;

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Miczek et al. 2002; Miczek et al. 2007b; Nelson and Chiavegatto 2001; Quadros et al. 2009b). The venerable serotonin deficiency hypothesis as simplifying principle, linking low serotonin activity to the propensity to engage in aggressive behavior, is yielding to a more differentiating interpretation of the accruing data (de Boer and Koolhaas 2005; Miczek et al. 2007b). The current review highlights several emerging themes of the past decade.

First, the dimension of impulsive aggressive behavior is a heritable trait that runs in families and appears amplified by salient experiences during a critical postnatal developmental period. The genetic architecture for synthetic and metabolic enzymes, receptor and particularly transporter molecules in serotonergic neurons provides ample targets for important life events to ultimately promote increased impulsive aggressive behavior (Caspi et al. 2002).

Second, superimposed on the serotonergic tone, plastic changes in the impulse flow in serotonin pathways to the forebrain are evident while an individual anticipates an aggressive or defensive act (Ferrari et al. 2003). As aggressive experiences accumulate, neuroadaptive changes in serotonergic dorsal raphé cells projecting to terminals in the forebrain are manifested in serotonin impulse flow and particularly in receptor regulation. These forms of neuroplasticity in serotonergic projections to the prefrontal cortex appear important for anticipating and preparing for imminent aggressive or defensive acts.

Third, one site of regulatory influences on cellular activity in the dorsal raphé nuclei (DRN) is the population of somatodendritic autoreceptors, and stimulation of these receptors inhibits impulse flow in serotonergic cells which, in turn, decreases escalated aggressive behavior in rodent models. Repeated somatodendritic autoreceptor stimulation or antagonism have been explored in order to enhance clinical management of affective disorders, including dysfunctions in social intercourse.

Fourth, excitatory and inhibitory transmitters such as glutamate and GABA synapse with serotonergic cells in the dorsal raphé nuclei, and the modulation of serotonergic activity by these inputs profoundly impacts aggressive behavior. Several members of the GABA and glutamate receptor subtypes, located on serotonergic cells, have already been identified as key targets for several drugs such as alcohol and benzodiazepines in their escalating and inhibiting effects on aggression.

Fifth, among the many peptides that modulate serotonin at the somata and terminals, CRF, vasopressin and opioid peptides are noteworthy for their profound effect on social and aggressive behavior. In rodent models, CRF1 receptor antagonists effectively and selectively reduce alcohol-heightened aggression by action on serotonergic neurons in the DRN, although these findings await translation into the clinic.

The last decade has seen also a concerted effort to translate more readily preclinical and clinical findings as is evident by two developments (1) an increasing focus on escalated types of aggressive behavior in animal models and (2) by operationally and functionally defined aggressive behaviors in clinical assessments.

## 2. Definition of Aggression

Most psychopharmacological research on serotonin and aggression is motivated by gaining insights into pathological aggression, both in human and veterinary medicine (Volavka et al. 2005). When working with laboratory models of animal aggression, it is useful to consider the ethological foundation of aggressive behavior such as its phylogenetic and ontogenetic origins and its functional significance for the individual and the species. Aggressive behavior comprises communicative signals, acts and postures for the purpose of obtaining a

specific goal or in defense against threatening stimuli (Miczek et al. 2002). These behaviors occur in the context of competing for food and other resources that are important to an individual's survival and reproduction (resident-intruder aggression), defense of a territory or offspring (territorial and maternal aggression), or in response to fear or frustration (Miczek et al. 2001). In this sense, the occurrence of aggressive behavior raises the fitness of the individual and enhances the survival of the species. For example, resident-intruder confrontations may represent male-male rivalries, establishing and maintaining a dominance hierarchy (Figure 1). So-called isolation-induced aggression captures many elements of a resident who excludes other breeding males from the territory (Brain and Benton 1979; Miczek et al. 2001; Table 1).

Based on distal and proximal antecedent conditions, the behavioral topography, and the consequences, aggressive behavior can be differentiated as offensive or defensive (Blanchard and Blanchard 1977; Brain 1979). In rats, a set of specific defensive behaviors occurs in response to either predator or conspecific attack, and comprises escape, freezing, defensive postures and threats (Blanchard et al. 2003; Pellis and Pellis 1988; Rasia-Filho et al. 2008). Defensive behaviors can be a response to threatening or fear-provoking stimuli and, usually, result in escapes (Brain 1979). For example, maternal aggressive behavior is seen in postpartum female rodents in order to protect offspring against male intruders, and this type of aggression includes both defensive and offensive elements (Lucion and de Almeida 1996; Parmigiani et al. 1998).

Violence in animals is a controversial term in animal ethology. This term has been hypothesized to be related to escalated, pathological and abnormal forms of aggression characterized by rapid attack latencies, prolonged and frequent aggressive behavior and attack bites (Miczek et al. 2002; Miczek et al. 2003). These parameters are quantitative, in that violence is expected to show shorter attack latencies and higher frequencies and longer durations of consummatory behavior than adaptive aggression. Measures of a qualitative nature have been proposed independently, where violence is considered qualitatively different from adaptive aggression. For instance, attach bites aimed at vulnerable parts of the opponent's body are considered characteristic of abnormal aggression (Haller et al. 2005). A few additional qualitative facets have been studied, namely lack of ritualistic behaviors as measured by Attack/Threat (A/T) ratios (Haller et al. 2005) and context independent attacks (Koolhaas 1978) aimed at the opponent regardless of its sex or state (free-living/ anaesthetized/dead) or the environment (home/neutral cage). In that sense, violence can therefore in principle refer to an escalated (hyper-) aggression (quantitative) or to an abnormal form of aggression (qualitative), or even to aggression that is both escalated and abnormal (both), which is unsurprisingly rare (for review see Natarajan and Caramashi 2010).

Aggressive behaviors in humans share commonalities with those in non-human animals, but they differ from most of them in their complexity. While social norms set the boundaries of appropriate aggressive behavior, inappropriate aggressive behavior in the form of interpersonal violence represents serious mental and social problems (Ferris et al. 2008). Aggressive behavior is a symptom in several psychiatric diseases, as detailed in the DSM-IV R and the updated DSM-V which is scheduled for publication in 2012, such as schizophrenia, brief reactive psychosis, anxiety disorder, adjustment disorder, impulse control disorder, antisocial personality disorder, attention deficit disorder, mania/depression, PTSD, autism, and substance abuse (Boles and Miotto 2003; Raine 2002; Rydén et al. 2009; Volavka et al. 2005).

A useful scheme considers human aggression as defensive, premeditated (e.g., predatory and instrumental) or impulsive-hostile in nature (Stoff and Vitiello 1996; Vitiello and Stoff

1997). Especially the premeditated and impulsive types of aggressive behaviors are diagnosed as pathological (i.e. in need of treatment). A converging pattern of empirical data links impulsive, but not premeditated, aggression to biological, environmental, and also to pharmacological or psychological treatment response factors (Coccaro et al. 2010).

Methodologically (see Table 2), human aggressive behavior as a state is assessed using protocols according to which individuals are provoked in competitive situations with fictitious opponents and that provide opportunities to engage in measurable aggressive responses (for review see Miczek et al. 2002). The assessment of aggressive traits in human subjects are accomplished by psychometric measures like inventories, questionnaires and scales. These laboratory measures of aggressive behavior have been used successfully in research on the role of 5-HT (Table 2). A critical challenge for this and similar experimental approaches is to relate the laboratory measures of aggression to aggressive and violent acts outside of the laboratory. It also remains difficult to discern subtypes of human aggression with laboratory measurement techniques. Table 2 summarizes the psychometric instruments which identify individuals with contrasting aggressive traits such as the impulsive-reactive-hostile-affective subtype versus the controlled-proactive-instrumental-predatory subtype (Stoff and Vitiello 1996).

## 3. Aggressive “trait” vs. “state”

Based on early clinical and preclinical studies, the most frequently reiterated hypothesis links a serotonin deficiency to individuals presenting impulsive, hostile, and violent behavior (Brown and Goodwin 1986; Goldman et al. 1992; Lesch and Merschdorf 2000; Linnoila and Virkkunen 1992; Mann 1999; Valzelli 1977). These individuals may benefit particularly from pharmacological treatments aimed at inhibiting 5-HT transporters (using SSRIs such as fluoxetine, citalopram), or activating 5-$HT_{1A}$ (buspirone) or blocking 5-$HT_{2A}$ receptors (risperidone). Acutely, these drugs induce *phasic* changes in 5-HT function that are associated with their transient anti-aggressive effects. Using *in vivo* microdialysis techniques, transient changes in 5-HT extracellular levels can be monitored before, during, after and in anticipation of an aggressive encounter in rats. In one study, reduced 5-HT levels in the prefrontal cortex were revealed during and after the aggressive confrontation, while no changes in 5-HT were detected in another terminal region, the nucleus accumbens (Van Erp and Miczek 2000; Figure 2). By contrast, chronic treatment with these anti-aggressive compounds may promote yet to be defined neuroadaptive changes in 5-HT function that are associated with the emergence of therapeutic effects (*e.g.*, autoreceptor desensitization).

On the other hand, genetic studies focus on aggression as a “*trait*”. While it is clear that these aggressive *traits* are polygenic, it is remarkable that in several cases a gene-environment interaction is required for the increased propensity to engage in violent outbursts, as observed with TPH2, MAO-A and 5-HTT polymorphisms (see below). For example, a SNP in TPH2 gene (A2051C) has been shown to have a link to aggressive behavior in rhesus monkeys. Individuals that have an AA/AC genotype show increased aggressive acts compared to those with a CC genotype when they were reared without their mother (peer-reared). This difference disappeared when individuals of both genotypes were reared by their mothers (Chen et al. 2010). In this review, we will discuss the effects of genes on aggressive behaviors with a focus on the interaction with salient environmental events.

In addition, gene-gene interactions are also of interest and need to be examined in the future. For example, Passamonti et al. (2008) showed interactions between 5-HTT and MAOA polymorphisms, and those interactions exerted stronger effects on the activity of the anterior

cingulate cortex, one of the brain areas implicated in impulsivity, including impulsive aggression. Many other genes may have subtle effects on aggressive phenotypes and it is possible that those genes have complex epistatic interactions from which stronger effects emerge (Miczek et al. 2001). In rodents, most genetic studies on aggression in the past 15 years make use of conventional knockout techniques in which the expression of a gene is generally deleted in the whole body, affecting all developmental stages and inducing compensatory changes in other genes (trait-like change; see Table 3). Novel tools, including conditional knockout, viral vector microinfusion, or drug-induceable knockout technique, can produce transient and local changes in gene expression, enabling the examination of more "phasic" changes in gene expression and how they affect aggressive behavior. The use of these techniques may reduce some discrepancies in the results from genetic and pharmacological studies of 5-HT function in aggression.

## 4. 5-HT receptors

### 4.1. Pharmacology of 5-HT receptors and aggression

So far, most evidence implicates the 5-$HT_1$ and 5-$HT_2$ families of receptors in aggressive behaviors (Miczek et al. 2002; Olivier 2004), with some initial evidence for the involvement of 5-$HT_3$ receptors as well (McKenzie-Quirk et al. 2005; Ricci et al. 2004; Rudissaar et al. 1999).

Clinically, the 5-$HT_{1A}$ receptor partial agonist buspirone can reduce aggressive behavior in mentally retarded patients (Kavoussi et al. 1997; Ratey et al. 1991). This compound has been used for the management of aggressive outbursts associated with neuropsychiatric disorders in adults and children (Connor and Steingard 1996; Pabis and Stanislav 1996). However, clinical studies have mostly focused on patients with multiple diagnoses and clinical symptoms, undergoing treatment with various drugs simultaneously (Brahm et al. 2008; Levy et al. 2005; Pabis and Stanislav 1996; Ratey et al. 1989; Ratey and O'Driscoll 1989). Thus, more controlled studies for different clinical populations are necessary to assess the efficacy – and side effect profile – of buspirone and other 5-$HT_{1A}$ agents as selective anti-aggressive medications. In preclinical investigations, systemic administration of 5-$HT_{1A}$ receptor agonists promotes anti-aggressive effects in several species, including fish, amphibian, birds, rodents, guinea pigs and non-human primates (Bell and Hobson 1994; Blanchard et al. 1988; Clotfelter et al. 2007; de Boer et al. 1999; de Boer et al. 2000; de Boer and Koolhaas 2005; Dompert et al. 1985; Haug et al. 1990; Joppa et al. 1997; Lindgren and Kantak 1987; McMillen et al. 1988; Miczek et al. 1998b; Muehlenkamp et al. 1995; Nikulina et al. 1992; Olivier et al. 1992; Sanchez et al. 1993; Sperry et al. 2003; Ten Eyck 2008; Tompkins et al. 1980). Only one exception was observed in fruit flies (*Drosophila melanogaster*), in which treatment with the 5-$HT_{1A}$ agonist, 8-OH-DPAT, escalated aggressive behavior (Johnson et al. 2009). Selective antagonists of 5-$HT_{1A}$ receptors, such as WAY-100635, block the anti-aggressive effect of 5-$HT_{1A}$ agonists, while having no reliable effects on aggression *per se* (de Boer and Koolhaas 2005; Mendoza et al. 1999; Miczek et al. 1998b).

Laboratory studies have found that the anti-aggressive effects of 5-$HT_{1A}$ agonists in vertebrates are consistently accompanied by non-specific effects including sedation, slow motor routines, stereotypic behavior or reduced social interest (de Boer and Koolhaas 2005; Miczek et al. 1998b; Olivier et al. 1995). However, some 5-$HT_{1A}$ agonists, at least in a ferally derived rat strain, can selectively reduce aggressive behavior without affecting other non-aggressive behaviors, (*i.e.*, alnespirone and S-15535; (de Boer et al. 1999; de Boer et al. 2000; de Boer and Koolhaas 2005). It is possible that those compounds act on a subpopulation of 5-$HT_{1A}$ receptors to exert this anti-aggressive effect, and thereby are more behaviorally specific.

Despite the absence of clinically approved drugs, preclinical work suggests that targeting 5-$HT_{1B}$ receptors may have more specific anti-aggressive effects than 5-$HT_{1A}$ manipulations. In mice and rats, the systemic administration of 5-$HT_{1B}$ agonists reduces aggressive behavior without sedation, or motor or sensory impairment (de Almeida et al. 2001; de Almeida and Miczek 2002; de Boer and Koolhaas 2005; Fish et al. 1999; Miczek et al. 2002; Miczek et al. 2004; Olivier et al. 1990; Olivier 2004; Figure 3). These effects were antagonized by the 5-$HT_{1B/1D}$ antagonist GR-127935, further confirming the involvement of 5-$HT_{1B}$ in mediating the anti-aggressive effects (de Boer and Koolhaas 2005). However, differences in the binding domain of 5-$HT_{1B}$ receptors of humans and rodents may yield different pharmacological selectivity and specificity of 5-$HT_{1B}$ agonists (Olivier 2004).

Determination of the critical brain regions and specific mechanisms underlying the anti-aggressive effects of 5-$HT_{1A}$ and 5-$HT_{1B}$ receptor agonists still remains to be resolved (Table 4). Neurobiological studies have associated the effects of 5-$HT_{1A}$ and 5-$HT_{1B}$ agonists with reduced 5-HT neuronal firing and release in projection sites (Adell et al. 2001; Bonvento et al. 1992; Sprouse and Aghajanian 1987), suggestive of presynaptic mechanisms mediating the anti-aggressive effects of these drugs. Activation of 5-$HT_{1A}$ and 5-$HT_{1B}$ inhibitory autoreceptors in the dorsal raphé nucleus (DRN) with microinfusion of selective receptor agonists consistently reduced aggressive behavior in rats and mice, but with concomitant reduction of motor activity and social interactions (Bannai et al. 2007; Faccidomo et al. 2008; Mos et al. 1993; Van Der Vegt et al. 2003). Infusion of a 5-$HT_{1A}$ agonist into the median raphé nucleus (MRN) also reduced aggressive behavior of lactating female rats (de Almeida and Lucion 1997).

The overall relevance of presynaptic mechanisms for the anti-aggressive effects of these manipulations is challenged by several reports that lesions or depletion of 5-HT neurons (e.g., using tryptophan hydroxylase inhibitor PCPA, or the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT)) do not affect the anti-aggressive effects of 5-$HT_{1A}$ and 5-$HT_{1B}$ agonists (de Almeida et al. 2001; Miczek et al. 1998b; Sanchez and Hyttel 1994; Sijbesma et al. 1991). While these data suggest postsynaptic 5-$HT_1$ receptors as critical sites of action, these pharmacological depletions spared a subpopulation of receptors.

In projection sites of 5-HT neurons, 5-$HT_{1B}$ receptors likely modulate 5-HT release from synaptic terminals as autoreceptors, whereas both 5-$HT_{1A}$ and 5-$HT_{1B}$ receptors modulate postsynaptic neurons (Olivier et al. 1992). In most studies, local activation of 5-$HT_{1A}$ and 5-$HT_{1B}$ in projection regions (e.g., medial preoptic area, lateral septum, orbitofrontal cortex, anterior hypothalamus, medial hypothalamus, periacqueductal gray) promote reduction of aggressive behavior under different procedures and species (see Table 4). Interestingly, under conditions that may promote escalated aggression, such as consumption of moderate doses of alcohol or maternal aggression, a 5-$HT_{1B}$ or 5-$HT_{1A}$ agonist further increased levels of aggressive behavior when infused into the medial prefrontal cortex (Faccidomo et al. 2008) or the medial septal area (de Almeida and Lucion 1997), respectively. Further studies are required to delineate the mechanisms for such pro-aggressive effects.

Atypical antipsychotic agents (*e.g.*, risperidone) with significant antagonist action at 5-$HT_{2A}$ receptors have been successfully used to reduce aggressive outbursts in patients diagnosed with various neuropsychiatric disorders (Buckley et al. 1997; Buitelaar et al. 2001; Czobor et al. 1995; De Deyn et al. 1999; Fava 1997; Keck, Jr. et al. 2000; Zarcone et al. 2001). On the contrary, some reports cast doubt on these routine uses of antipsychotics (Swanson et al. 2008; Tyrer et al. 2008). The placebo treatment group showed the greatest recovery from aggressive challenges compared to antipsychotic drug groups in people with intellectual disability (Tyrer et al. 2008). In animal models, risperidone and other drugs with more selective action as 5-$HT_{2A}$ antagonists (e.g., ketanserin, ritanserin and MDL 100907) reduce

aggressive behaviors in a behaviorally non-specific manner (Rodriguez-Arias et al. 1998; Sakaue et al. 2002; Shih et al. 1999; White et al. 1991).

Activation of 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors by DOI and other substituted phenylisopropylamines also reduce aggressive behavior in several species including flies, amphibians, mice and rats (Bonson et al. 1994; de Almeida and Lucion 1994; Johnson et al. 2009; Muehlenkamp et al. 1995; Olivier et al. 1995; Sanchez et al. 1993; Ten Eyck 2008). However, the effects of 5-$HT_2$ ligands are accompanied by sedative effects in the same dose range as the anti-aggressive effects. Local infusion of 5-$HT_{2A/2C}$ agonist into the PAG reduces maternal aggression in rats (de Almeida et al. 2005), whereas microinjections into the medial hypothalamus and into the PAG increased defensive aggression in cats (Hassanain et al. 2003; Shaikh et al. 1997; see Table 4). This latter effect is likely linked to the role of 5-$HT_{2A/2C}$ receptors in anxiety-like behavior (Lucki and Wieland 1990; Nogueira and Graeff 1995). The development of more selectively acting pharmacological tools will allow a more adequate differentiation of 5-$HT_2$ receptor subtypes, and promises to dissociate the anti-aggressive and sedative effects.

### 4.2. Genetics of 5-HT receptors and aggression

The 5-$HT_{1B}$ receptor is the first molecule that has been linked to aggression by using the genetic knockout technique. Male mice with disrupted 5-$HT_{1B}$ receptor expression (Htr1b$^{-/-}$) increased aggressive behavior in the resident-intruder test relative to wild-type residents after a month of isolation (Saudou et al. 1994; Table 3; but see Bouwknecht et al. 2001). However, due to very low, close to zero, aggressive behavior in the wild-type mice (129/Sv-ter), the number of attacks in Htr1b$^{-/-}$ was very low and the latency to initiate was very long compared to other strains of mice. These mice displayed behavioral disinhibition in other behavioral tests including hyperlocomotor activity (Brunner et al. 1999; Ramboz et al. 1995), drug intake (Crabbe et al. 1996; Rocha et al. 1998), measures of anxiety-like behavior (Brunner et al. 1999; Malleret et al. 1999), and autonomic hyperreactivity to novelty (Bouwknecht et al. 2001). Females of Htr1b$^{-/-}$ also show increased aggressive behavior during the postpartum period (Brunner and Hen 1997). These results have been interpreted to suggest a role for 5-$HT_{1B}$ receptors in the inhibition of aggressive and impulsive behaviors.

Linkage analysis on a SNP in the 5′UTR region of the 5-$HT_{1B}$ gene, A161T, found a significant correlation between this SNP and the history of aggression in subjects who completed violent suicides (Zouk et al. 2007). Individuals with the T161 locus had higher lifetime aggressive behaviors. T161 polymorphism had reduced transcriptional activity of 5-$HT_{1B}$ receptor (Sun et al. 2002), and thus lower 5-$HT_{1B}$ receptor expression may be related to lifetime aggression in suicidal victims. By contrast, other SNPs in the 5-$HT_{1B}$ showed an opposite pattern. A linkage study of 5-$HT_{1B}$ with alcoholism and antisocial personality disorder showed that the G861C polymorphism had significant linkage with antisocial alcoholism in two groups (Lappalainen et al. 1998). Specifically, C861, the SNP with higher 5-$HT_{1B}$ receptor expression (Huang et al. 1999), was related to antisocial behavior in alcoholics. However, these associations between the 5-$HT_{1B}$ polymorphisms (G861C, G261T, or C129T) and aggression/antisocial behavior are not seen in other studies (Huang et al. 1999; Kranzler et al. 2002; Sinha et al. 2003; Van den Berg et al. 2008). Therefore, findings from pharmacological manipulation, genetic deletion and polymorphism studies of the 5-$HT_{1B}$ receptor do not follow a simple and consistent scheme. This suggests that the role of 5-$HT_{1B}$ receptors may depend on the types of aggressive behaviors or tonic and phasic level of aggression.

In contrast to the important role of 5-$HT_{1A}$ receptors in the neural control of aggressive behavior based on pharmacological evidence, no prominent linkage has been reported with

polymorphisms in the 5-$HT_{1A}$ gene and aggression so far. However, there is evidence for a correlation between 5-$HT_{1A}$ receptor expression and aggression. A human PET study found a higher 5-$HT_{1A}$ receptor distribution in prefrontal cortex of subjects with higher aggression scores based on a self-report questionnaire (Witte et al. 2009). Also, rats selected for higher defensive reactions showed reduced 5-$HT_{1A}$ receptor expression in several brain areas (Popova et al. 1998). It is possible that the polymorphisms which directly or indirectly affect 5-$HT_{1A}$ receptor transcription may be associated with either aggressive or defensive responses. 5-$HT_{1A}$ receptor knockout mice engaged in less aggressive behavior relative to wild-type controls, which also implicates the possible involvement of the 5-$HT_{1A}$ gene in aggressive behavior (Zhuang et al. 1999; Table 3). Given the consistent pharmacological data on anti-aggressive effects of 5-$HT_{1A}$ agonists in clinical and preclinical studies, lack of complementary genetic data remains disconcerting.

Platelet 5-$HT_{2A}$ receptor binding is increased in patients with personality disorders and in a psychiatric population with greater lifetime aggression scores (Coccaro et al. 1997; McBride et al. 1994). In postmortem brains, lifetime aggression was positively correlated with prefrontal 5-$HT_{2A}$ receptor binding in suicide victims (Oquendo et al. 2006). Therefore, it is possible that polymorphisms that affect the level of expression of 5-$HT_{2A}$ receptors can be associated with self-directed aggression. In some samples, significant linkage was found between polymorphisms in the 5-$HT_{2A}$ receptor, T102C, A1438G and His452Tyr, and aggressive-impulsive trait or adolescent-onset antisocial behavior in humans (Assal et al. 2004; Bjork et al. 2002; Burt and Mikolaiewski 2008; Nomura et al. 2006). But others have reported no such link between aggression and 5-$HT_{2A}$ polymorphisms (Khait et al. 2005; Van den Berg et al. 2008). Again, the success with pharmacotherapeutic management of aggressive patients using compounds with affinity for 5-$HT_{2A}$ receptors would suggest that violence-prone individuals may be characterized by distinctive 5-HT polymorphisms.

## 5. 5-HTT

### 5.1. Pharmacology of 5-HTT and aggressive behavior

Blocking serotonin transporter molecules is effective in reducing and preventing aggressive behavior in humans and non-human animals, presumably due to increased brain 5-HT levels. Clinically, blocking 5-HT transporters with the administration of selective serotonin reuptake inhibitors (SSRIs), reduces aggressive outbursts and violent behavior in psychiatric patients (Barkan et al. 2006; Blader 2006; Bond 2005; Coccaro and Kavoussi 1997; New et al. 2004; Reist et al. 2003; Walsh and Dinan 2001), with therapeutic effects being usually observed after chronic treatment (>3 weeks). However, there are occasional reports that SSRIs may facilitate aggressivity and suicidal behavior, and the causes for these unusual outcomes remain to be determined (Spigset 1999; Troisi et al. 1995).

In animal models, both acute and chronic treatment with SSRIs can dose-dependently reduce aggressive behavior (Carrillo et al. 2009; Delville et al. 1996; Olivier et al. 1989; Pinna et al. 2003). Acute administration of several SSRIs (e.g., fluoxetine, fluvoxamine, sertraline) reduced aggression in different contexts and species, including rodents and non-human primates (Carrillo et al. 2009; Cutler et al. 1997; Delville et al. 1996; Fairbanks et al. 2001; Ferris et al. 1997; Fuller 1996; Ho et al. 2001; Sanchez and Meier 1997). Chronically, daily treatment with the SSRI citalopram abolished the escalated levels of aggression induced by a moderate dose of alcohol over the course of three weeks, with modest reductions in baseline levels of aggression in mice (Caldwell and Miczek 2008; Figure 4). On the other hand, chronic SSRI treatment may restore competent agonistic behavior in placid, non-aggressive laboratory rats (Mitchell et al. 1991; Mitchell 2005; Mitchell and Redfern 1992; Mitchell and Redfern 1997). Thus, the anti-aggressive effects of SSRIs are more prominent in

conditions of escalated aggressive behavior such as those promoted by alcohol (Caldwell and Miczek 2008).

Mechanistically, acute or chronic administration of citalopram (or the more potent isomer escitalopram) both elevate extracellular levels of 5-HT in the prefrontal cortex of rats, suggesting increased cortical 5-HT as a putative therapeutic mechanism for SSRIs' effects on aggression and other mood disorders (Ceglia et al. 2004). However, the anti-aggressive effects of another SSRI, fluoxetine, might be primarily mediated by actions on neurosteroids and GABA transmission, and only secondarily via 5-HT (Pinna et al. 2003; Pinna et al. 2006). Furthermore, long-term effects of SSRIs likely recruit pre- and post-synaptic mechanisms and neuroplastic events that contribute to their therapeutic effects (Benmansour et al. 1999; Blier and de Montigny 1998; Ceglia et al. 2004; Pineyro et al. 1994).

### 5.2. Genetics of 5-HTT and aggressive behavior

A variation in the length of 5′-flanking transcriptional control region (promoter) of the 5-HTT gene (the serotonin-transporter-gene-linked polymorphic region; 5-HTTLPR) has been identified in humans (Heils et al. 1996), great apes and rhesus monkeys (Lesch et al. 1997). This variation affects the transcriptional activity of the 5-HTT gene, and the short length (*s*) allele reduces 5-HTT expression in vitro and lowers the prolactin response to clomipramine in human, which reflects reduced 5-HT function, compared to the homozygote of long length allele (*l/l*) (Heils et al. 1995; Lesch et al. 1996; Whale et al. 2000). An association study in humans showed that individuals with one or two copies of the *s* allele (*s/s, s/l*) were characterized by higher anxiety, depression, hostility and aggression, and lower agreeableness than individuals of the *l/l* homozygote in both sexes (Lesch and Merschdorf 2000). Higher frequency of the *s* allele was observed in alcoholics accompanied with high impulsivity and antisocial behaviors (type 2 alcoholism) compared to alcoholics without antisocial behavior (type 1) or healthy controls (Hallikainen et al. 1999). Consistent with the human polymorphism, rhesus monkeys that possess the *s* allele engaged in higher rates of aggressive behaviors compared to *l/l* individuals (Jarrell et al. 2008; Lesch and Merschdorf 2000).

A genotype-environment interaction can be found in 5-HTT polymorphism. Rhesus monkeys with the *s* allele had lower 5-hydroxyindoleacetic acid (5HIAA) in CSF than *l/l* individuals when they were reared without their mother (peer-reared). This difference disappeared when both were reared by their mothers (Bennett et al. 2002). Peer-reared monkeys showed increased aggression-related behavior as well as altered CSF 5HIAA levels (Higley et al. 1991; Kraemer et al. 1989). In humans, higher suicide ideations or attempts were observed in individuals carrying the *s* allele than in *l/l* homozygotes when they encountered a number of stressful life events, but not in less stressful situations (Caspi et al. 2003). Therefore, it is possible that animals with the *s* allele are more vulnerable to the stressful challenges, and subsequently escalate their aggressive behaviors towards others and themselves. However, the effect of the *s* allele on aggression differed among sexes (Cadoret et al. 2003) and even cultures (Baca-Garcia et al. 2004).

Seemingly contrary results were observed in mice with a deletion of the 5-HTT gene (Slc6a4). Homozygote and heterozygote 5-HTT knockout mice on a C57BL/6J background showed fewer attack bites and longer latencies to start fighting relative to wild-type mice in the resident-intruder test (Holmes et al. 2002; Table 3). 5-HTT knockout mice have lower 5-HT uptake and higher extracellular 5-HT concentrations in the forebrain compared to wild-type (Mathews 2004). 5-HTT knockout mice underwent changes in more than 50 phenotypes including morphological, physiological, sensory, and behavioral functions (Murphy and Lesch 2008), and thus those pleiotropic changes of other phenotypes may contribute to the reduction of aggressive behaviors in these mice. Comparable findings on 5-

HTT and aggression were reported in the rat. 5-HTT knockout rats on a Wistar/Crl background also showed reduced offensive behaviors and longer attack latencies compared to wild-type rats (Homberg et al. 2007). Therefore, genetic ablation of 5-HTT consistently reduced aggressive behaviors in rodents.

## 6. Monoamine oxidase A (MAOA)

### 6.1. Pharmacology of MAOA and aggression

Inhibition of MAOA reduces the oxidative metabolism of monoamines, thus presumably increasing the availability of 5-HT and other monoamines in the brain. Despite the early recognized importance of MAO inhibitors as antidepressants, there are only a few preclinical studies that systematically evaluated the effects of MAO inhibitors on aggression (Miczek 1987). For the most part, non-selective inhibitors of both MAOA and MAOB (*e.g.* phenelzine, isocarboxazid, tranylcypromine) show acute anti-aggressive effects in doses that also alter motor and other non-aggressive behaviors (DaVanzo et al. 1966; Sofia 1969; Valzelli et al. 1967; Welch and Welch 1968). Clinically, non-selective MAO inhibitors or selective MAOB inhibitors can be useful in the pharmacological management of personality disorders that include impulsive aggression and suicidal tendencies as important symptoms, but are accompanied by an unfavorable profile of side effects (Hollander 1999; Raj 2004).

### 6.2. Genetics of MAOA and aggression

The gene for MAOA was the first candidate identified as a determinant in the susceptibility for aggression in humans, and it has remained the focus of most genetic and epigenetic studies. Brunner and colleagues (Brunner et al. 1993b) identified a large Dutch kindred with a syndrome of borderline mental retardation and dysregulated impulsive aggression. All affected males showed aggressive outbursts, and some exhibited sexually aberrant behavior, attempted murder and arson. Linkage and sequence analyses showed that all affected males in this family possessed one missense mutation in the MAOA gene on the X chromosome, so that MAOA function was completely disturbed (Brunner et al. 1993a). The affected males had higher serotonin and lower metabolites of NE, DA, and 5-HT in the urine (Brunner et al. 1993a). MAOA also is of significance in the probability of fighting in animals. Male mice with disrupted MAOA gene on either C3H/He or 129Sv background showed escalated aggressive behaviors compared to wild-types, as is evident by skin wounds among the cage-mates and a short latency to initiate attacks in the resident-intruder test (Cases et al. 1995; Scott et al. 2008). MAOA-deficient mice also showed a large increase in 5-HT and NE, and a subtle DA elevation, in the brain and liver (Cases et al. 1995; Kim et al. 1997; Table 3). It is likely that the change of 5-HT function is the cause of the behavioral changes in the MAOA-deficient mice. Ketanserin and MDL100907, antagonists that preferentially bind to $5\text{-HT}_{2A}$ receptors, blocked the escalated aggression in the MAOA mutant mice (Shih et al. 1999). Depletion of 5-HT by PCPA during the early developmental stage improved some behavioral and brain structural abnormality in the MAOA-deficient mice (Cases et al. 1995; Cases et al. 1996).

Variable-number tandem repeat (VNTR) polymorphism, which exists on the upstream region of the MAOA gene, regulates MAOA expression depending on the number of repeats: Alleles with 3.5 or 4 repeats have 2-10 times higher transcription than 3 or 5 repeat alleles in vitro (Denney et al. 1999; Sabol et al. 1998). A prominent interaction between MAOA genotype and environment on aggressive behavior has been reported (Caspi et al. 2002; Figure 5). Under stressful rearing conditions, such as abuse or neglect, or exposure to traumatic life events in the first 15 years of their lives, individuals with low MAOA expression (MAOA-L) polymorphisms showed higher propensity to have criminal arrests and a violent history, adolescent conduct disorder, and also higher aggressive disposition in

self-report questionnaire compared to individuals with higher MAOA expression (MAOA-H) allele or MAOA-L individuals without abuse (Caspi et al. 2002; Foley et al. 2004; Frazzetto et al. 2007; Kim-Cohen et al. 2006; Weder et al. 2009; Widom and Brzustowicz 2006). If rearing environments were lumped together, the effect of MAOA genotype disappeared (Fresan et al. 2007) or sometimes MAOA-H individuals reported higher aggression using data from interviews and questionnaires (Manuck et al. 2000; Manuck et al. 2002). Therefore, individuals with MAOA-L allele are vulnerable to environmental factors and show a high propensity to engage in aggressive behaviors only when they are in a stressful environment. These findings are consistent in males, but not in females (Sjoberg et al. 2007). Similarly, rhesus monkeys have a repeat length variation polymorphism (rhMAOA-LPR) in the MAOA gene, and this polymorphism is also linked to aggression. Monkeys with a low-activity allele exhibited higher aggressive behavior and tend to attain higher dominance rank when they were reared by their mother. In contrast, when they were reared separately from their parents (peer-reared), monkeys with the low-activity allele engaged in less aggressive behavior (Newman et al. 2005). This inhibition of aggression has been attributed to increased fear and anxiety in peer-reared monkeys (Higley and Suomi 1986).

Neuroimaging studies have indicated pronounced differences in volume and activity of limbic system and neocortical areas between individuals with MAOA-L and MAOA-H (see Buckholtz and Meyer-Lindenberg 2008 for a review). fMRI analysis in healthy human volunteers showed that MAOA-L males had smaller limbic and orbitofrontal volumes, and higher activity in amygdala and hippocampus during aversive recall (Meyer-Lindenberg et al. 2006), that may be related to violent behavior in MAOA-L individuals. Alia-Klein et al. (2008) reported that lower MAOA activity in cortical and subcortical brain areas is associated with high aggression measured by self-report questionnaire, independent from MAOA polymorphism. These data show that the MAOA activity is one of the determinants for the vulnerability to aggression, especially the interaction between MAOA polymorphism and salient social experiences can escalate the aggression and also change relevant brain structures.

## 7. Modulation of serotonergic activity by other systems

The 5-HT neurons in the raphé nuclei are modulated by other amines, acids, peptides and steroids (Adell et al. 2002). Recently, several efforts were undertaken to uncover the nature of the neural systems that modulate 5-HT neurons to promote escalated aggressive behaviors. Here we will focus briefly on inhibitory and excitatory neurotransmitters and some neuropeptides in terms of their interaction with 5-HT system. The more general role of those molecules on aggressive behavior was reviewed recently (Miczek et al. 2007b).

### 7.1 GABA

The inhibitory neurotransmitter γ-aminobutyric acid (GABA) plays a crucial role in the modulation of the dorsal raphé nuclei (DRN). Large number of GABA interneurons and distal GABAergic afferents can be found in the DRN (Belin et al. 1983; Gervasoni et al. 2000; Nanopoulos et al. 1982; Wang et al. 1992), and both $GABA_A$ and $GABA_B$ receptors are expressed in the DRN (Bowery et al. 1987). *In vitro* electrophysiology studies have shown that the activation of the $GABA_A$ and $GABA_B$ receptors on the 5-HT neurons both inhibit 5-HT cell firings (Colmers and Williams 1988; Gallager and Aghajanian 1976; Innis and Aghajanian 1987; Judge et al. 2004). On the other hand, *in vivo* microdialysis studies have shown that the $GABA_A$ and $GABA_B$ receptors in the DRN differentially modulate 5-HT release depending on the projection sites (Tao et al. 1996). We recently found that the pharmacological activation of $GABA_B$ receptors in the DRN escalated aggressive behaviors in mice (Takahashi et al. submitted). Interestingly, only under the influence of alcohol, local

administration of $GABA_A$ receptor agonist muscimol also heightened aggressive behaviors (Takahashi et al. 2010). By contrast, intra-DRN muscimol inhibited aggressive behaviors in rats (Van Der Vegt et al. 2003) or was without effect on aggression in the absence of alcohol (Takahashi et al. 2010). Therefore, both subtypes of GABA receptors are involved in escalated forms of aggressive behavior via different mechanisms. *In vivo* microdialysis showed that $GABA_B$ activation in the DRN increased extracellular 5-HT level in the medial prefrontal cortex (Takahashi et al., submitted; Figure 6). This result suggests that the *phasic* activation of 5-HT system may be able to promote certain types of escalated aggressive behaviors in mice.

### 7.2 Glutamate

The DRN receives prominent glutamate input by the descending projections from the lateral habenula, periaqueductal gray, lateral hypothalamus, interpeduncular nucleus and medial prefrontal cortex (Aghajanian and Wang 1977; Behzadi et al. 1990; Kalen et al. 1986; Maciewicz et al. 1981). Both the N-metyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolaproprionate/kainate (AMPA/kainate) are localized on serotonergic neurons and increase the 5-HT release in the DRN and its projection areas (Celada et al. 2001; Pallotta et al. 1998; Tao et al. 1996; Tao and Auerbach 2000; Vandermaelen et al. 1986). Systemic administrations of classic antagonists of NMDA receptors, including phencyclidine (PCP) and dizocilpine (MK-801), can increase aggressive behavior (Burkhalter and Balster 1979; Krsiak 1974; McAllister 1990; Musty and Consroe 1982; Rewerski et al. 1971; Wilmot et al. 1987), while other studies find that these compounds are suppressive and sedative due to their strong side-effects (Belozertseva and Bespalov 1999; Lang et al. 1995; Miczek and Haney 1994; Tyler and Miczek 1982). Anatomically discrete analysis is required to identify the sites of action for NMDA receptors that produce enhanced aggressive behavior. The 5-HT system is one of the candidates, especially the descending glutamatergic projection from the medial prefrontal cortex (mPFC) to the DRN will be interesting to investigate. The prefrontal cortex (PFC) has been implicated in the emotion regulation including aggression (Davidson et al. 2000; Miczek et al. 2007a). This PFC-DRN glutamatergic projections are involved in the controllability or emotion regulation (Amat et al. 2005) and further study will be required to address the role of this PFC-DRN glutamatergic neurons on aggressive behaviors.

### 7.3 CRF

The DRN is innervated by Corticotropin-Releasing Factor (CRF) immunoreactive fibers, and presents both subtypes of CRF receptors, $CRF_1$ and $CRF_2$ (Chalmers et al. 1995; Potter et al. 1994; Swanson et al. 1983). Evidence suggests that CRF, CRF receptors and other peptides of the CRF family (Urocortins), play key modulatory roles on DRN serotonin neurons (see Valentino and Commons 2005). Electrophysiological and microdialysis studies consistently report that i.c.v. or intra-DRN microinjections of CRF, or drugs targeting CRF receptors, exert potent modulatory control over 5-HT neural firing (Kirby et al. 2000; Lowry et al. 2000), and 5-HT output to limbic, striatal and prefrontal cortical regions (Amat et al. 2004; Amat et al. 2005; Forster et al. 2008; Lukkes et al. 2008; Meloni et al. 2008; Price et al. 1998; Price and Lucki 2001).

A role for CRF, $CRF_1$ and $CRF_2$ receptors in aggressive behavior has been indicated by studies on maternal- and inter-male aggression in mice and hamsters (D'Anna et al. 2005; Farrokhi et al. 2004; Gammie et al. 2004; Gammie et al. 2005; Gammie et al. 2007; Gammie and Stevenson 2006). In rats, there is evidence that low doses of CRF themselves may facilitate or induce pro-aggressive effects after i.c.v. or intra-amygdala infusions (Elkabir et al. 1990; Tazi et al. 1987). Under conditions of escalated aggression promoted by moderate doses of alcohol in male mice, $CRF_1$ receptors are a promising target for pharmacological

intervention. Systemically, antagonists of $CRF_1$ receptors reduce alcohol-heightened aggression, but also reduce baseline levels of aggressive behavior (Quadros et al. 2009a). When locally administered into the DRN, $CRF_1$ antagonists (e.g., CP-154526 or MTIP) prevent the escalated levels of aggression observed after consumption of alcohol, with no side effects on other behaviors. Remarkably, such anti-aggressive effects of $CRF_1$ antagonists can be abolished with the infusion of 8-OH-DPAT into the DRN, which transiently slows 5-HT impulse flow. On the other hand, microinfusion of a $CRF_2$ antagonist (Astressin-2B) into the DRN escalates aggressive behavior (Quadros et al. 2009a).

Thus, the modulation of aggressive behaviors by CRF systems depends on the species (mice, rats) and type of aggression (species-typical, maternal or escalated aggression). Initial evidence suggests the 5-HT cells in the DRN as one of the critical sites for such modulation in the escalated aggression promoted by alcohol, with presumably opposing roles for $CRF_1$ and $CRF_2$ receptors.

### 7.4. Vasopressin

Arginine vasopressin (AVP) is a neuropeptide that modulates a variety of social behaviors including pair-bonding, social recognition, maternal behavior, and aggression (Albers and Bamshad 1998; Coccaro et al. 1998; Ferris 1992; Goodson 2008; Koolhaas et al. 1990; Neumann et al. 2010; Winslow et al 1993). Selective antagonist of vasopressin V1a receptors (SRX251, [d(CH2)5Tyr(Me)AVP]) inhibited inter-male aggression (Ferris et al. 2006; Ferris and Potegal 1988), indicating the involvement of V1a receptors in aggressive behaviors. The interaction between AVP and 5-HT has been shown to be critical for certain types of aggressive behaviors. In humans, a positive correlation has been observed between AVP concentrations in the CSF and the life history of aggression, a composite measure of trait aggression. Also, there was a positive correlation between AVP concentrations and prolactin responses to a challenge with d-fenfluramine (Coccaro et al 1998). This result indicates that individuals that have higher aggression ratings tend to have a high AVP concentration in the CSF and a hyporesponsive 5-HT system. Neuronal interactions between AVP containing neurons and 5-HT neurons are found in the anterior hypothalamus (Ferris et al. 1997; Ferris et al. 1999), and this AVP-5-HT link is implicated in aggression. Microinjection of AVP into the anterior hypothalamus increased aggressive behavior in hamsters, and systemic fluoxetine (5-HTT inhibitor) treatment blocked the pro-aggressive effect of AVP (Delville et al. 1996; Ferris et al. 1997). Therefore, 5-HT may have an inhibitory function on the AVP induced heightened aggression. In contrast, mice with disrupted Ca2+ channel expression (Cav2−/−) showed escalated level of aggressive behavior and also higher AVP concentration in the CSF. However, these animals showed overactivation of the dorsal raphe 5-HT neurons and increased 5-HT concentration in the hypothalamus (Kim et al. 2009). Further investigation is anticipated to uncover how AVP and 5-HT interact and whether there are specific types of aggression that require the activity of either 5-HT or AVP systems independently.

## 8. Other molecules that directly or indirectly affect 5-HT pathways and aggression

Here we will briefly discuss selected molecules that directly or indirectly affect serotonergic pathways and modulate aggressive behaviors based mainly on findings from gene knockout mouse studies, as summarized in Table 3. For more reviews on genes and aggressive behavior, see Maxson and Canastar (2007), Miczek et al. (2001) and Nelson and Chiavegatto (2001).

### 8.1. Pet-1 (also known as Fev)

Pet-1, one of the transcription factors, is specifically expressed in the serotonergic raphé neurons, and has a critical role in 5-HT neural development. Deletion of Pet-1 expression reduced 5-HT level in the forebrain, and also depleted expression of TPH, 5-HTT, and the vesicular monoamine transporter 2 (Vmat2). In the resident-intruder test, Pet-1 knockout mice (Pet-1−/−) engaged in higher frequency and intensity of attacks toward a conspecific male (Hendricks et al. 2003). These increases in aggressive behavior in Pet-1−/− mice are embedded in broad behavioral disruptions that extended to maternal and anxiety-like behaviors (Hendricks et al. 2003; Lerch-Haner et al. 2008), and it is possible that those other behavioral changes promote indirectly aggressive behaviors.

### 8.2. Brain-derived neurotrophic factor (BDNF)

BDNF has several important roles in the neuron including neuronal survival, development, differentiation and plasticity. Mice with decreased BDNF expression including knockout (BDNF+/−) and conditional knockout (BDNF2L/1LNes-cre and BDNF2L/2LCk-Cre) all showed increased inter-male aggression (Chan et al. 2006; Lyons et al. 1999). Higher hippocampal extracellular levels of 5-HT were observed in BDNF+/− mice compared to wild-type (Deltheil et al. 2008), but fluoxetine reduced their heightened aggressive behavior (Lyons et al. 1999). All mutants changed 5-$HT_{2A}$ receptor expression, however BDNF+/− showed increased 5-$HT_{2A}$ expression in the lateral frontal cortex and hypothalamus (Lyons et al. 1999) whereas BDNF2L/1LNes-Cre and BDNF2L/2LCk-Cre exhibit reduced 5-$HT_{2A}$ receptor expression in the prefrontal cortex (Chan et al. 2006; Rios et al. 2006). A SNP in the BDNF gene, Val66Met, has attracted strong interest because of its association with mood disorders and hippocampal function in humans (Egan et al. 2003; Neves-Pereira et al. 2002). Knock-in mice with this human Met allele also showed an increased aggressive behavior and changed the response to SSRI treatment (Chen et al. 2006). In contrast to the consistent results on aggressive behavior among BDNF mutant mice, studies on polymorphisms of the BDNF gene in aggressive behavior in humans remain to be resolved. No association was observed between Val66Met polymorphism and proneness to violence in a Chinese male sample (Tsai et al. 2005). Other SNPs in the BDNF gene may be associated with high impulsivity in children with ADHD (Oades et al. 2008).

### 8.3. Neuronal nitric oxide (nNOS)

Nitric oxide, a free radical gas which diffuses across membranes, is involved in several cellular functions (for review see Calabrese et al. 2007). Mice lacking neuronal nitric oxide synthase (nNOS−/−) show various deficits in their physiological development and also behavior (Huang et al. 1993). nNOS−/− males, but not females, showed higher duration of aggressive behavior and also displayed much fewer submissive postures compared to wild-types (Nelson et al. 1995). Serotonergic dysfunction was observed in the nNOS−/− mice, specifically reduced 5-HT turnover in the brain and deficient 5-$HT_{1A}$ and 5-$HT_{1B}$ receptor function (Chiavegatto et al. 2001). Escalated aggression in the nNOS−/− was rescued by 5-HTP treatment which increased 5-HT level and turnover. These findings point to an important role of nitric oxide for the normal 5-HT function, and thus increased aggression nNOS−/− may be induced by changing 5-HT activity.

### 8.4. Neuropeptide Y (NPY)

NPY controls primarily food intake, energy balance, and metabolic regulation (Herzog 2003). This molecule which is critical for energy homeostasis is also implicated in aggressive behavior (Emeson and Morabito, 2005). Male mice with deleted expression of the Y1-receptor (Y1−/−) showed obesity and reduced energy homeostasis (Kushi et al. 1998), and also exhibited increased aggressive behaviors in the resident-intruder test (Karl et

al. 2004). However, this escalated aggression in Y1−/− was observed only in the home cage, not in the novel environment. This result suggests a specific increase in territorial aggression which may be related to altered 5-HT function of Y1−/− (Karl et al. 2004). TPH mRNA expression in the raphé nuclei was reduced in the Y1−/− mice. In addition, 5-$HT_{1A}$ agonist treatment reduced escalated aggression in Y1−/− mice.

### 8.5. α-Calcium-Calmodulin Kinase II (α-CaMKII)

α-CaMKII is a neural specific enzyme and has been shown to be involved in long-term potentiation (LTP; Silva et al. 1992). Heterozygotes of α-CaMKII knockout mice showed escalated defensive aggression but not offensive aggression (Chen et al. 1994). In the resident-intruder test, resident α-CaMKII heterozygotes showed aggressive behavior similar to wild-type mice. In contrast, when the mutant was tested as an intruder, they exhibited high defensive reactions toward the resident. Reduced 5-HT release was observed in the dorsal raphé of α-CaMKII mutants in vitro, and thus the changed 5-HT function may be associated with defensive aggression in this mouse.

Gene targeting techniques in mice have identified a number of genes involved in aggressive behaviors (Table 3) and these animals offer insights into the simple serotonin-aggression link. The direction of the change in the 5-HT system is not always the same (Table 3); some knockout mice that showed escalated aggressive behaviors also showed a reduction in 5-HT tone (e.g. Pet1, nNOS, NPY, α-CaMKII) but others showed a clear increase of 5-HT release in the brain (e.g. MAOA, BDNF, $Ca_v2.2$). Further examination of 5-HT changes in dissected brain regions and also of changes in specific 5-HT receptor subtypes in these knockout mice will clarify more details of the serotonin-aggression link.

## 9. Concluding Remarks

In summary, understanding the complex role of 5-HT in aggression requires consideration of multiple factors, including (1) the type of aggressive behavior, its topography and function, (2) the genetic background of the individual and the typical phenotype for this background, (3) the trait characteristics of the human subject or the mouse (*i.e., Mus musculus* are a pugnacious species and many inbred strains are quite placid), and (4) the situational conditions under which aggressive behaviors has been engendered. From a clinical perspective, the impulsive, hostile, explosive type of aggressive behavior is part of a more broadly defined trait that has been linked to profound changes in the expression of MAO-A, 5-HTT, and 5-HT receptors. A growing number of studies that suggest important gene-environment interactions involving genes that regulate 5-HT transmission (e.g., monoamine oxidase and serotonin transporters) and stressful life events are of particular interest. When associated, these conditions are critical in determining an increased vulnerability to initiate violent acts and aggressive outbursts (e.g., Bennett et al. 2002; Caspi et al. 2002; Caspi et al. 2003). By associating the specific characteristics of the individual, the environment and the type of social interaction, the serotonin-aggression link can be further explored, providing new pharmacological and molecular targets for interventions.

From a therapeutic perspective, it seems clear that manipulations of 5-HT transmission are effective for the management of aggressive behavior, despite the common observation of side effects. Traditionally, pharmacological manipulations that increase 5-HT function are effective in reducing aggression in clinical and preclinical settings. However, whether such increases in 5-HT transmission are the main relevant mechanism for the anti-aggressive effects remains in dispute. For example, agonists of the 5-$HT_1$ family of receptors and citalopram (SSRI) promote opposite changes in extracellular concentrations of 5-HT in terminal regions, despite both having anti-aggressive effects. Such observations suggest that drugs acting at different 5-HT molecular targets may recruit different neuropharmacological

mechanisms in order to promote their anti-aggressive effects, likely involving actions on specific receptor subpopulations and downstream signaling pathways. Of particular clinical interest, the development of neuroplastic changes seems to accompany the emergence of anti-aggressive effects after chronic treatment with SSRIs. More recently, the identification of pharmacological targets that directly or indirectly modulate 5-HT function, such as receptors for glutamate, GABA and neuropeptides, show promising results for more selective anti- and pro-aggressive effects.

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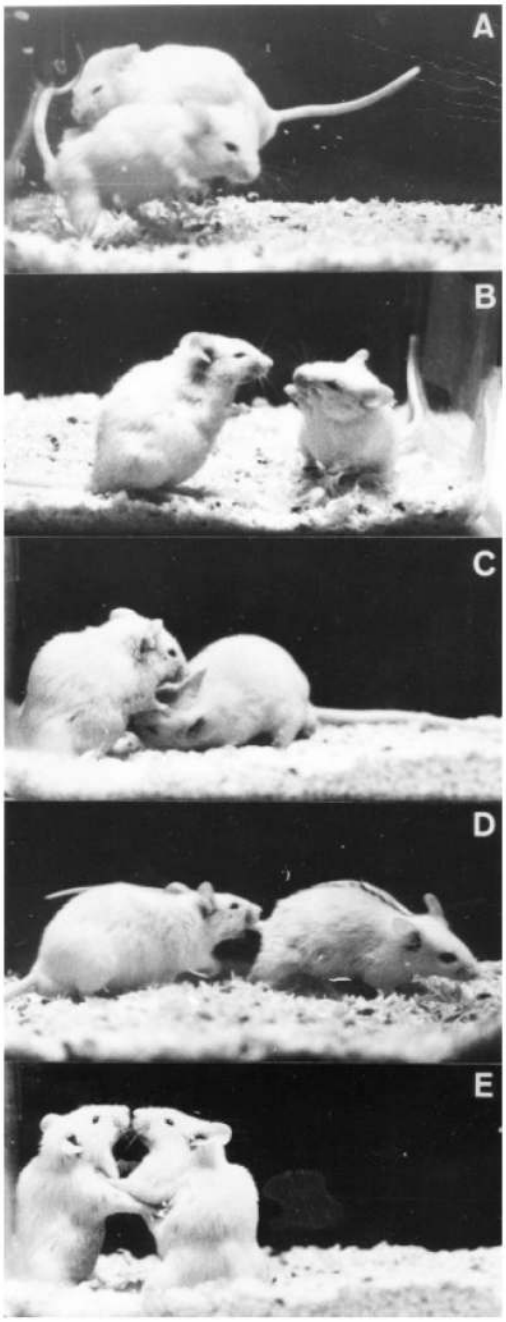


**Figure 1. Mouse agonistic behavior**

Behaviors of resident and intruder mice engaged in an aggressive confrontation: (a) the resident leaps and bites the intruder as the intruder attempts to escape; (b) the resident (*right*) threatens as the intruder (*left*) holds a defensive upright posture; (c) the resident investigates the intruder's anogenital region; (d) the resident pursues the fleeing intruder; (e) both resident and intruder engage in a mutual upright defensive posture. *Reprinted with permission from* Miczek and O'Donnell (1978).

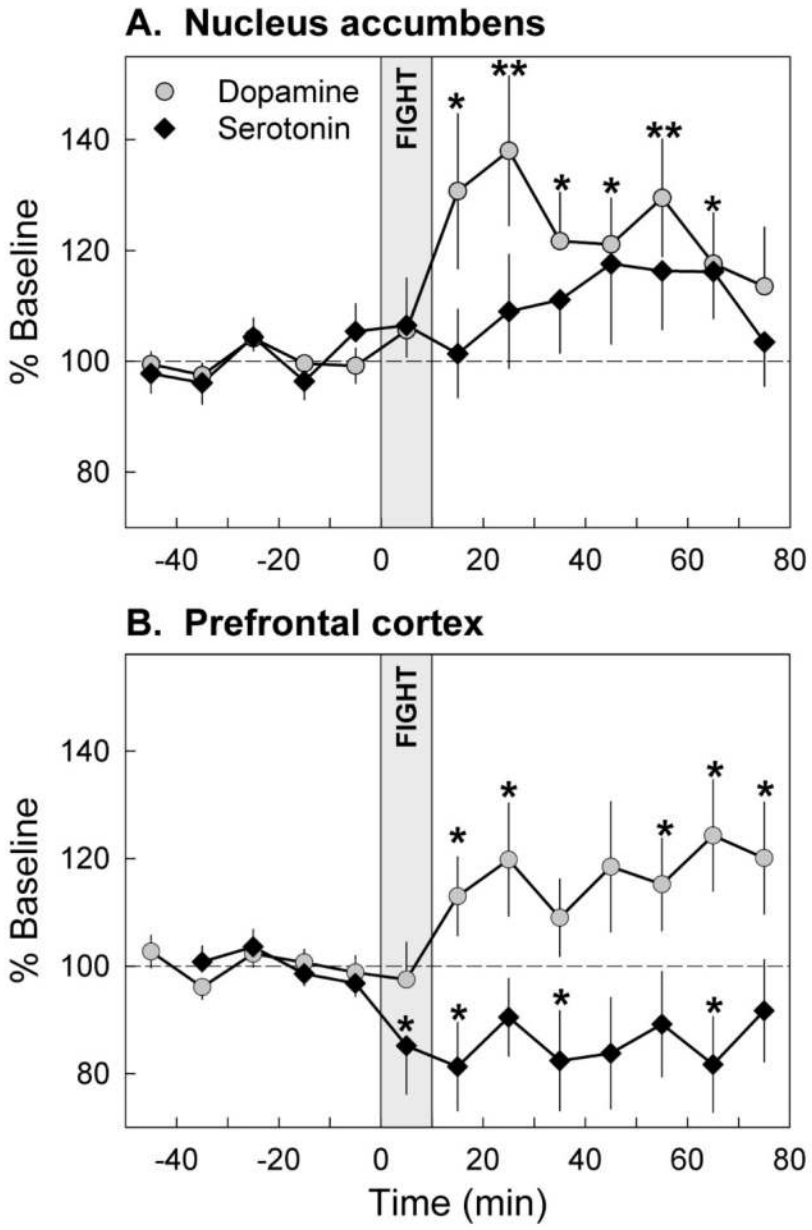


**Figure 2. Dopamine and serotonin during aggression**

Measurements of extracellular dopamine and serotonin via *in vivo* microdialysis in resident male rats before, during, and after a confrontation with an intruder. (a) In the nucleus accumbens (*top panel*), dopamine levels (*gray circles*) rise and remain elevated after the confrontation, while serotonin levels (*black diamonds*) do not significantly change. (b) In the prefrontal cortex (*bottom panel*), dopamine levels rise after the confrontation, while serotonin decline and remain lower after the confrontation. Samples were collected every 10 min and levels are expressed as mean percent of baseline ± SEM. Baseline was measured for 50 min before the fight. The vertical light gray bar indicates the occurrence of the 10-min fight. * and ** represent significant differences from baseline (*dashed line*) at the $p < 0.05$ and $p < 0.01$ levels, respectively. *Reprinted with permission from* Van Erp and Miczek (2000).

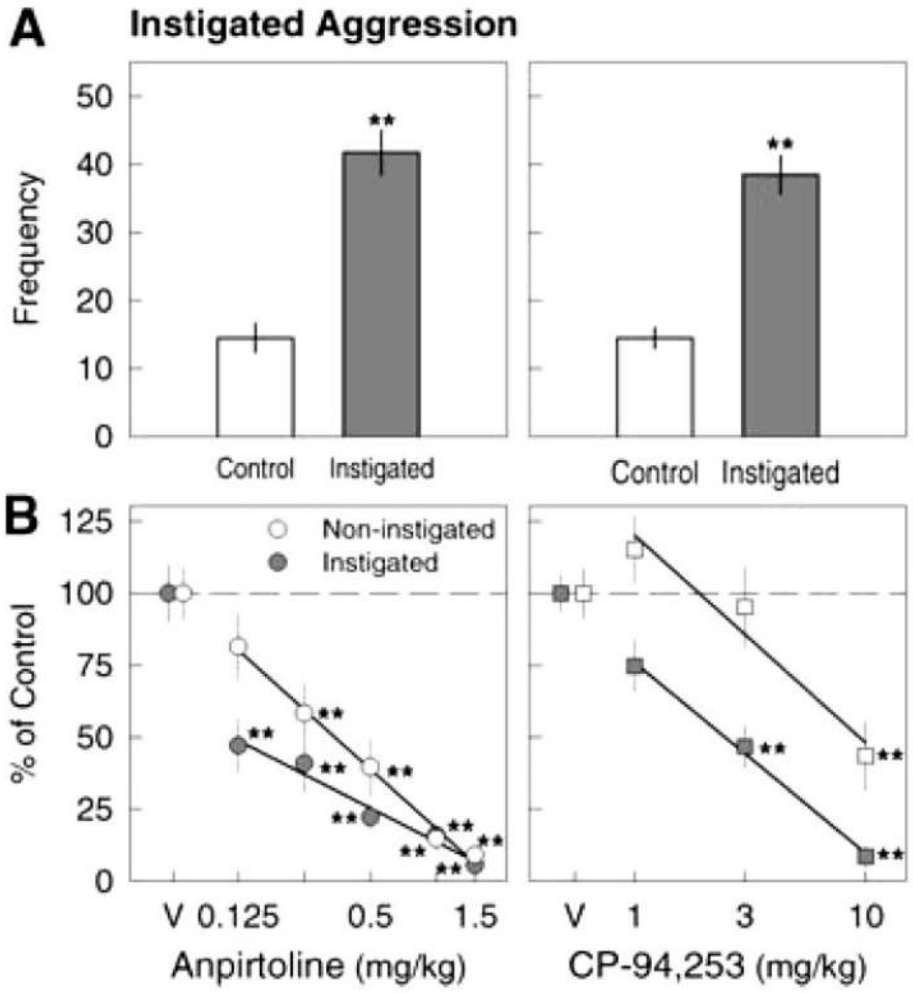


**Figure 3.**

***A***. Effects of social instigation on aggressive behavior by a resident mouse toward a male intruder. Bars represent the mean frequency ±SEM (*vertical lines*) of attack bites under control (*light gray*) and instigated (*dark gray*) conditions. Asterisks denote statistical significance from control (**P<0.01). ***B***. Preferential reduction of instigated aggressive behavior by the 5-HT1B agonist anpirtoline (*left panel, filled circles*) and CP-94,253 (*right panel, filled squares*). Symbols represent the mean frequency of attack bites, expressed as a percentage of vehicle (*V*) baseline, ±SEM. Light gray symbols represent non-instigated fighting and dark gray symbols represent instigated levels of fighting. Asterisks denote significance from vehicle baseline (P<0.05). *Adapted from* Fish et al. (1999) *and* de Almeida and Miczek (2002).

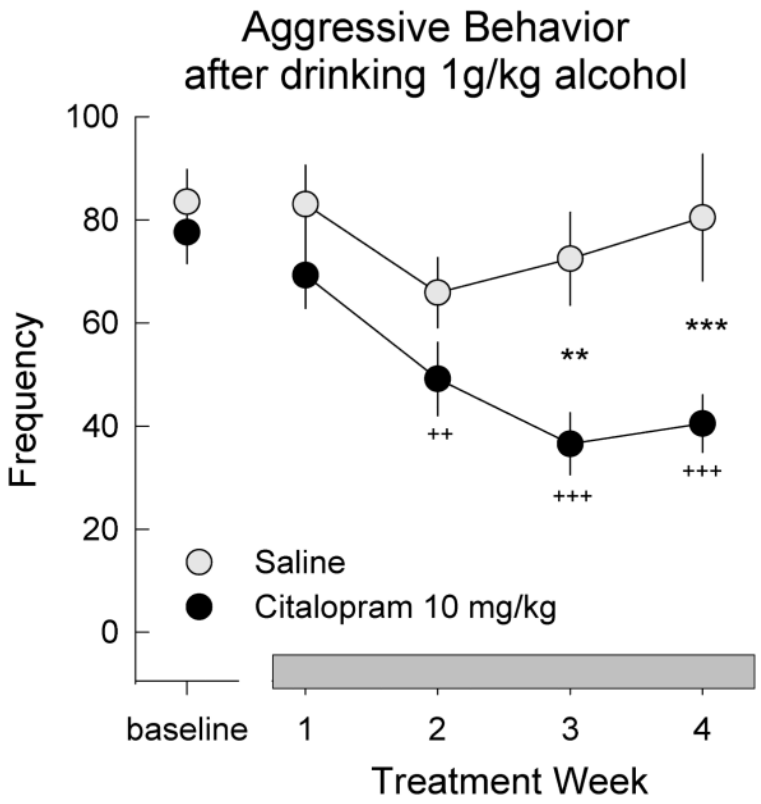


**Figure 4.**

Effects of repeated, twice daily administration of the SSRI citalopram (10 mg/kg, i.p.) on aggressive behavior in mice after drinking 1.0 g/kg alcohol in operant self-administration panels. Frequency of aggressive acts (± SEM) is defined as sum of attack bites, threats, pursuits and tail rattles, and was analyzed in 5 min confrontations against a male intruder, during the course of fours weeks of citalopram (or saline control) treatment. + symbols represent differences from baseline (++ $p<0.01$; +++ $p<0.001$); * symbols represent group (citalopram vs. saline-controls) differences (** $p<0.01$; *** $p<0.001$). *Adapted from* Caldwell & Miczek (2008).

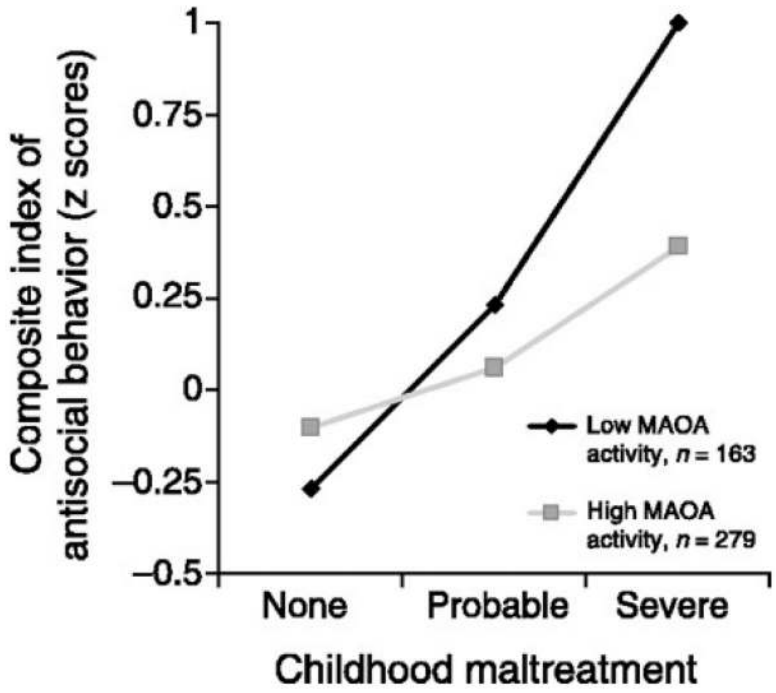


**Figure 5.**
Means on the composite index of antisocial behavior as a function of MAOA activity and a childhood history of maltreatment. MAOA activity is the gene expression level associated with allelic variants of the functional promoter polymorphism, grouped into low and high activity; childhood maltreatment is grouped into 3 categories of increasing severity. The antisocial behavior composite is standardized (z score) to a M = 0 and SD = 1; group differences are interpretable in SD unit differences (d). *Reprinted with permission from* Caspi et al. (2002).

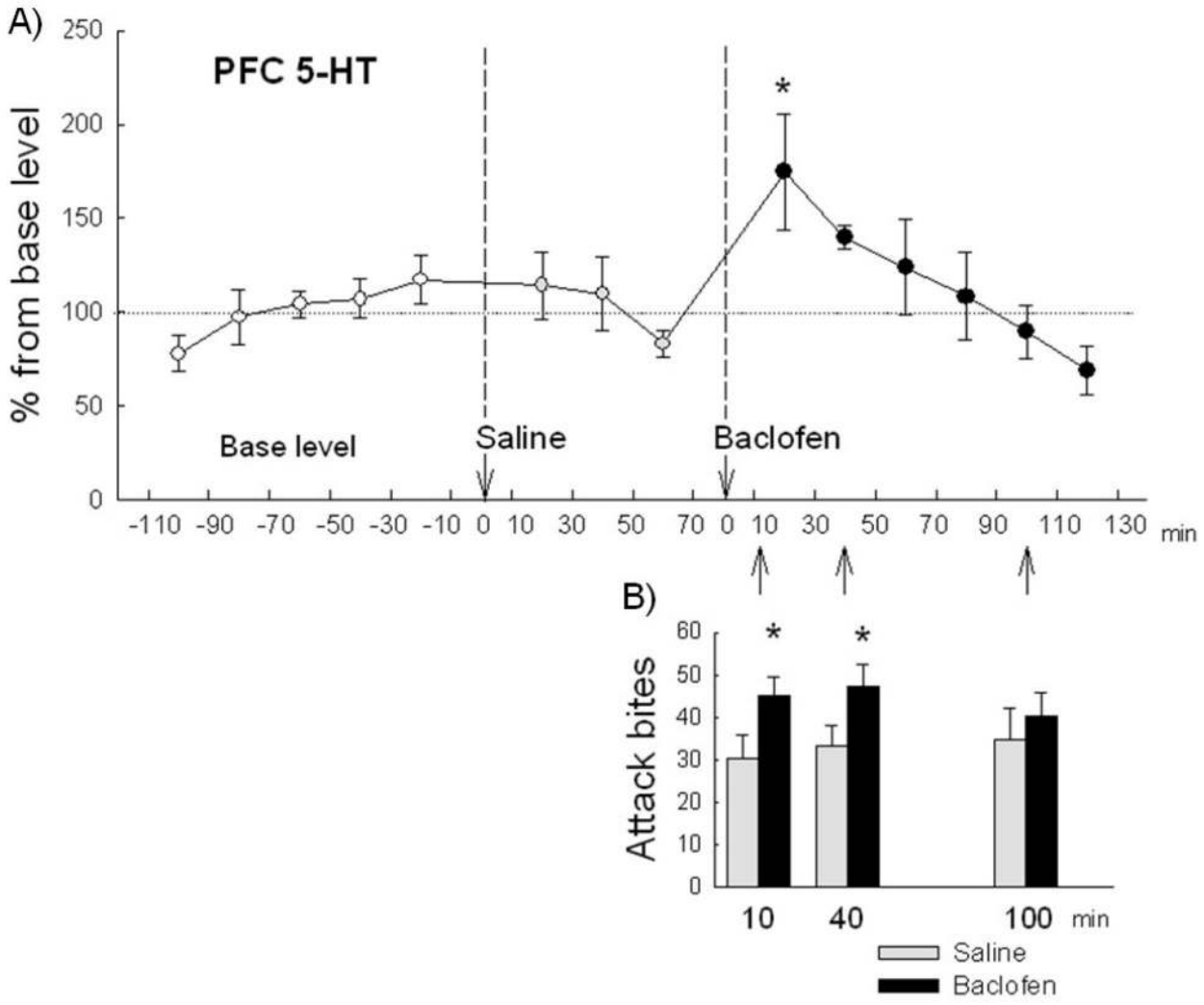


**Figure 6. Extracellular 5-HT concentration in the medial prefrontal cortex (mPFC) of mice after $GABA_B$ receptor activation in the dorsal raphe nucleus (DRN)**

(A) Baclofen microinjected into the DRN increased the 5-HT level in the mPFC whereas saline injection did not change the 5-HT level. Twenty minutes samples were collected 5 samples for baseline, 3 samples after saline injection, and 6 samples after baclofen (0.06 nmol) injection. Data are expressed as percentage of baseline (n=7). * $p<.05$ compared to the baseline. (B) The effect of 0.06 nmol baclofen on attack bites after the different interval (10, 40 and 100 min, corresponding to the time period of fraction 9, 11, and 14 in the microdialysis, respectively). Escalated attack bites were observed both 10 and 40 minutes after the intra-DRN baclofen injection. * $p<.05$ compared to corresponding vehicle control.

## Table 1
## Types of aggressive behavior in preclinical models

| **A. Species-typical aggressive behavior** | | | |
|---|---|---|---|
| | **Situational or Experimental variable** | **Agonistic behavioral measurements** | **References** |
| **Dominant resident**, mainly in primates and rats | In a stable colony where dominance hierarchy is to be established and maintained. | Frequency and duration of agonistic acts, postures, and displays including supplants, threat, pursue, and fight. | Mehlman et al. 1994<br>Higley et al. 1996<br>Fairbanks et al. 1999<br>Bennett et al. 2002<br>Bernstein et al. 1974<br>Steiniger 1950<br>Vandenbergh 1967 |
| **Territorial resident** (*resident-intruder* test), mainly in mice and hamsters | Requires an established territory. In the laboratory, home-cage of experimental male (*resident*) where it is pair-housed with a female. A male stimulus animal (*intruder*) that is group housed with other males is introduced into resident's cage. | Frequency of attack bite, sideways threat, tail-rattle, pursue, upright posture.<br>Latency to the first bite. | Van Oortmerssen and Bakker 1981<br>Eibl-Eibesfeldt 1950<br>Miczek and O'Donnell 1978<br>Crawley et al. 1975 |
| B**Maternal aggression**, mainly in rats, mice, and hamsters | Home-cage of lactating females from postpartum day 1 to 7. Either male or female of intruder is introduced into dam's cage. | Frequency of attack bite (especially directed at the snout and the face), sideways threat, tail-rattle, pursue, upright posture.<br>Latency to the first bite | Hurst 1987<br>Sgoifo et al. 1992<br>Lonstein and Gammie 2000<br>Noirot et al. 1975<br>Haney et al. 1989 |
| **Female aggression**, mainly in primates and rodents. | Dominant hierarchy among female monkeys.<br>In the laboratory settings, female rodent pair-housed with a breeding male. Sexually matured female is introduced as an intruder. | Harrassing attacks by dominant female. Frequency of attack bite, sideways threat, tail-rattle, pursue, upright posture.<br>Latency to the first bite | Smuts 1986<br>Palanza et al. 2005<br>DeBold and Miczek 1981<br>Zitzman et al. 2005 |
| **Isolation-induced** *aggression* (similar to territorial aggression) | Male isolated for same time, ranging from 24 h to 8 weeks prior to *resident-intruder* encounter. | Frequency of attack bite, sideways threat, tail-rattle, pursue, upright posture.<br>Latency to the first bite. | Malick 1979<br>Valzelli and Bernasconi 1979<br>Cairns and Nakelski 1971<br>Yen et al. 1959 |
| **B. Escalated aggressive behavior** | | | |
| | **Situational or Experimental variable** | **Agonistic behavioral measurements** | **References** |
| **Alcohol-heightened aggression**, mainly in rats and mice | Animals receive ethanol (1.0g/kg) intraperitoneally or orally before the resident-intruder encounter. | (These 3 methods measure aggressive behavior in same residentintruder method)<br>Frequency of attack bite, sideways threat, tail-rattle, pursue, upright posture.<br>Latency to the first bite<br>Targets of attack bites (head, dorsal areas, ventral areas, appendages) | Peeke and Figler 1981<br>Blanchard et al. 1987<br>Miczek et al 1992, 1998a<br>Miczek and de Almeida 2001 |
| **Social provocations** (instigations), mainly in hamsters, mice, and rats | A resident male pre-exposed to another breeding male in his home-cage without direct agonistic interaction (stimulus animals are behind protective screen), followed by resident-intruder encounter. | | Heiligenberg 1974<br>Potegal and Tenbrink 1984<br>Potegal 1991<br>Fish et al. 1999 |
| **Frustration-heightened** aggression | A resident male trained to obtain rewards. Before the resident-intruder encounter, reward is omitted. | | Berkowitz 1993<br>De Almeida and Miczek 2002 |
| **Aggression induced by low glucocorticoids** | Animals are adrenalectomized and implanted with a low corticosterone pellet | | Haller et al. 2001 |
| **Affective defense** ("rage"), mainly in cats | Electrical stimulation (0.2–0.8 mA, 63 Hz, 1 ms per half cycle duration) delivered in medial hypothalamus or midbrain periaqueductal gray. | Hissing, arching of the back, retraction of the ears, piloerection, unsheathing of the claws, papillary dilatation and paw striking | Leyhausen 1979<br>Siegel et al. 1999<br>Hess 1954 |

## Table 2
## Experimental protocols for assessing 5-HT effects on human aggressive behavior

| **A. Experimental manipulations** | | | |
|---|---|---|---|
| **Experimental Manipulation** | **Measurement** | **Trait/State** | **References** |
| Aggressive responses toward a competitor are measured in the form of electric shock settings | Activate buttons at 5–10 settings, each corresponding to a different intensity or duration of electric shock | State | Buss 1961<br>Godlaski and Giancola 2009 |
| A fictitious instigator or competitor is the target of aggressive responses that are measured in the form of electric shock deliveries | Setting of electric shock level on a scale from 1–10 | State | Taylor 1967<br>Chermack and Giancola 1997 |
| The subjects are provoked by having points subtracted that are earned in a competitive task. The point losses are attributed to a fictitious opponent, but are actually determined by a computer program according to a random schedule. Subjects responded by retaliation of point subtractions (= aggressive responses | Number of point subtractions from a fictitious competition | State | Cherek and Heistad 1971<br>Cherek and Lane 1999<br>Gowin et al. 2010 |
| Aggression was defined as delivery of electric shocks to a fictitious opponent | Use of a modified version of the Buss aggression machine. Setting of shock level on a scale from 1–5 | State | Zeichner and Pihl 1979<br>Giancola et al. 2009 |
| **B. Psychometric inventories** | | | |
| **Psychometric Assessment** | **Instrument** | **Trait/State** | **References** |
| Aggression, impulsive and hostility are measured by Minnesota Multiphasic Personality Inventory MMPI | Inventory | Trait | McKinley et al. 1948<br>Nagtegaal and Rassin 2004 |
| Buss-Durkee Hostility Inventory (BDHI), a self-rating scale of anger and hostility. 66 items with false/true answers; also contains 7 scales: assault, indirect aggression, irritability, negativism, resentment, suspicion and verbal aggression | Inventory | Trait | Buss and Durkee 1957 |
| Anger and anxiety are measured by State-Trait Anger Expression Inventory (STAXI) | Inventory | State/Trait | Spielberg et al. 1973<br>Kim et al. 2009b |
| Aggression is measured by Beck Anxiety Inventory and Beck Depression Inventory | Inventory | Trait | Beck et al. 1961<br>Lamar et al. 2009 |

## Table 3

### Genes and aggressive behavior in mice

| Gene | Abb | Chr | Background strain (Generations of backcross) | Type of aggression | Effects | Serotonin function | References |
|---|---|---|---|---|---|---|---|
| Plasmacytoma expressed transcript 1 | Pet1 (Fev) | 1 | Mix C57BL/6 and 129Sv | Isolation-induced resident aggression | Increased | 90% reduction of brain 5-HT | Hendricks et al. 2003 |
| Arginine vasopressin receptor 1B | V1bR | 1 | Mix C57BL/6 and 129/SvJ | Isloation-induced aggression | Suppressed | | Wersinger et al. 2002 |
| | | | | Neutral cage aggression | Suppressed | | |
| Aadenosine A1 receptor | A1AR | 1 | Mix C57BL and 129/OlaHsd | Isolation-induced resident aggression | Increased | | Gimenez-Llort et al. 2002 |
| Regulators of G protein signaling 2 | Rgs2 | 1 | C57BL/6J (N5) | Social dominance test | Suppressed | | Oliveira-dos-Santos et al. 2000 |
| v-abl Abelson murine leukemia viral oncogene homolog 2 (Abelson-related gene) | Arg | 1 | Mix C57BL/6 and 129/SvJ | Resident aggression | Suppressed | | Koleske et al. 1998 |
| Glutamic acid decarboxylase 2 | $GAD_{65}$ | 2 | Mix C57BL/6 and CBA2 | Isolation-induced resident aggression | Suppressed | | Stork et al. 2000 |
| Calcium channel, voltage-dependent, N type, α1B subunit | Cav2.2 | 2 | Mix C57BL/6J and 129S4/SvJae | Isolation-induced resident aggression | Increased | Increased hypothalamus 5-HT | Kim et al. 2009a |
| dopamine β-hydroxylase | Dbh | 2 | Mix C57BL/6J and 129/SvEv | Isolation-induced resident aggression | Suppressed | | Marino et al. 2005 |
| Brain-derived neurotrophic factor [+/−] | BDNF | 2 | C57BL/6J (>N10) | Isolation-induced resident aggression | Increased | Decreased brain 5-HT | Lyons et al. 1999 |
| β2-microglobulin | β2m | 2 | 129S2/SvPas (Mix C57BL/6J?) | Resident aggression | Suppressed | | Loconto et al. 2003 |
| Oxytocin | Oxt | 2 | Mix C57BL/6J and 129SvEv | Isolation-induced resident aggression | Increased | | Winslow et al. 2000 |
| | | | | Resident aggression | Increased | | |
| | | | | | Suppressed | | DeVries et al. 1997 |
| membrane metallo endopeptidase (enkephalinase) | NEP | 3 | Mix C57BL/6J and 129Sv | Resident aggression | Increased | | Fischer et al. 2000 |

| Gene | Abb | Chr | Background strain (Generations of backcross) | Type of aggression | Effects | Serotonin function | References |
|---|---|---|---|---|---|---|---|
| Cannabinoid receptor 1 | CB1 | 4 | CD1 (N15) | Isolation-induced resident aggression | Increased[1] | | Martin et al. 2002 |
| Preproenkephalin | Enk | 4 | Mix CD1 and 129 | Isolation-induced resident aggression | Increased[1] | | Konig et al. 1996 |
| endothelial nitric oxide synthase | eNOS | 5 | Mix C57BL/6 and 129Sv | Resident aggression | Suppressed | Increased 5-HT turnover | Demas et al. 1999 |
| | | | | Neutral cage aggression | Suppressed | | |
| Interleukin-6 | IL-6 | 5 | Mix C57BL/6, 129/SvEv | Isolation-induced resident aggression | Increased[2] | No difference in brain 5-HT concentration | Alleva et al. 1998 |
| Adrenergic receptor, α2c | $Na\alpha_{2C}$ | 5 | C57BL/6J (N7) | Isolation-induced resident aggression | Increased | | Sallinen et al. 1998 |
| Neuronal nitric oxide synthase | nNOS | 5 | Mix C57BL/6J, 129Sv, DBA2 | Resident aggression | Increased | Reduced brain 5-HT turnover | Nelson et al. 1995 |
| | | | | Maternal aggression | Suppressed | | Gammie and Nelson 1999 |
| Acetylcholinesterase | AChE | 5 | 129S6/SvEvTac | Home-cage hierarchy | Suppressed | | Duysen et al. 2002 |
| Adenylate cyclase activating polypeptide 1 receptor 1 | PAC1 | 6 | Mix C57BL/6J and 129Sv | Resident aggression | Suppressed | | Nicot et al. 2004 |
| Tachykinin receptor 1 | NK-1r | 6 | Mix C57BL/6 and 129Sv | Isolation-induced resident aggression | Suppressed | | De Felipe et al. 1998 |
| A cluster of vomeronasal receptor genes | $V1R_{a/b}$ | 6 | 129/SvEv | Maternal aggression | Suppressed | | Del Punta et al. 2002 |
| Oxytocin receptor | Oxtr | 6 | Mix C57BL/6 and 129Sv | Isloation-induced aggression | Increased | | Takayanagi et al. 2005 |
| | | | | Cage-mate injury | Increased | | |
| Histamine receptor H1 | H1 | 6 | Mix C57BL/6J and 129 | Isolation-induced resident aggression | Suppressed[2] | Increased 5-HT turnover | Yanai et al. 1998 |
| Amyloid β(A4) precursor proteinbinding, family A, member 2 | X11L | 7 | C57BL/6 | Competitive feeding | Subordinate | Increased Hypothalamus 5-HT | Sano et al. 2009 |
| Transient receptor potential cation channel, subfamily C, | TRP2 | 7 | Mix C57BL/6J and 129Sv | Resident aggression | Suppressed | | Stowers et al. 2002 |

| Gene | Abb | Chr | Background strain (Generations of backcross) | Type of aggression | Effects | Serotonin function | References |
|---|---|---|---|---|---|---|---|
| member 2 | | | | | | | |
| Neuropeptide Y receptor Y1 | Y1 | 8 | Mix C57BL/6 and 129SvJ | Resident aggression | Increased | Reduced TPH mRNA expression in the raphe nuclei | Karl et al. 2004 |
| Prostaglandin E receptor 1 (Subtype EP1) | EP1 | 8 | C57BL/6 (N5) | Neutral cage aggression | Increased | No difference in 5-HT turnover | Matsuoka et al. 2005 |
| Norepinephrine transporter | NET | 8 | Mix C57BL/6J and 129SvJ | Isolation-induced resident aggression | Increased[1] | | Haller et al. 2002 |
| Neural cell adhesion molecule 1 | NCAM1 | 9 | C57BL/6J (>N5) | Isolation-induced resident aggression | Increased | | Stork et al. 1997 |
| Aromatase (Cyp19a1) | Ar | 9 | Mix C57BL/6 and 129S/SvEv | Resident aggression | Suppressed | | Matsumoto et al. 2003 |
| | | | | Aggression toward female | Increased | | |
| 5-hydroxytryptamine (serotonin) receptor 1B | 5-HT$_{1B}$ | 9 | 129S2/SvPas | Resident aggression | Increased | Deleted 5-HT$_{1B}$ receptor expression | Saudou et al. 1994 |
| | | | | Maternal aggression | Increased | | Brunner and Hen 1997 |
| Estrogen Receptor-α | ERα | 10 | Mix C57BL/6J and 129 | Resident aggression | Suppressed | | Ogawa et al. 1998b |
| | | | | Female aggression | Increased | | Ogawa et al. 1998a |
| Fyn tyrosine kinase | Fyn | 10 | Mix C57BL/6 and CBA | Isolation-induced resident aggression | Suppressed | | Miyakawa et al. 2001 |
| nuclear receptor subfamily 2, group E, member 1 | Nr2e1 | 10 | C57BL/6J (>N6) | Resident aggression | Increased | | Young et al. 2002 |
| Adenosine A2a receptor | A2AR | 10 | CD1 (N4) | Isolation-induced resident aggression | Increased | | Ledent et al. 1997 |
| Tryptophan hydroxylase 2 | Tph2 | 10 | FVB/N (N7) | Home-cage injury | Increased | Reduced brain 5-HT | Alenina et al. 2009 |
| Glutamate receptor, ionotropic, AMPA1 (α1) | GluR-A | 11 | C57BL/6J (N5) | Isolation-induced aggression | Suppressed | No difference in brain 5-HT level | Vekovischeva et al. 2004 |
| | | | | Neutral cage aggression | Suppressed | | |
| 5-hydroxytryptamine (serotonin) transporter | SERT | 11 | C57BL/6J (N8) | Isolation-induced resident aggression | Suppressed | Increased extracelluler 5-HT | Holmes et al. 2002 |
| Estrogen Receptor-β | ERβ | 12 | Mix C57BL/6J and 129 | Resident aggression | Increased[1] | | Ogawa et al. 1999 |

| Gene | Abb | Chr | Background strain (Generations of backcross) | Type of aggression | Effects | Serotonin function | References |
|---|---|---|---|---|---|---|---|
| Dopamine transporter | DAT | 13 | Mix C57BL/6J and 129SvJ | Dyadic encounter aggression | Increased | | Rodriguiz et al. 2004 |
| 5-hydroxytryptamine (serotonin) receptor 1A | 5-HT$_{1A}$ | 13 | 129S1/Sv | Resident aggression | Suppressed | Deleted 5-HT1A receptor expression | Zhuang et al. 1999 |
| Catechol-O-methyltransferase 1 [+/−] | COMT | 16 | Mix C57BL/6J and 129SvJ | Neutral cage aggression | Increased | No difference in brain 5-HT level | Gogos et al. 1998 |
| Calcium/calmodulin-dependent protein kinase II alpha [+/−] | αCaMK II | 18 | Mix C57BL/6, 129/OU, BALB/c | Defensive aggression | Increased | Reduced 5-HT release in the dorsal raphe nucleus | Chen et al. 1994 |
| Melanocortin-5 receptor | MC5R | 18 | C57BL/6 (>N7) | Neutral cage aggression | Suppressed | | Morgan et al. 2004 |
| Monoamine oxidase A | MAOA | X | C3H/HeJ | Resident aggression | Increased | Increased brain 5-HT up to 9 fold | Cases et al. 1995 |
| | | | | Cage-mate injury | Increased | | |
| Cyclic nucleotide–gated channel a2 | Cnga2 | X | Mix C57BL/6J and 129SvEv | Resident aggression | Suppressed | | Mandiyan et al. 2005 |
| Guanosine diphosphate (GDP) dissociation inhibitor 1 | Gdi1 | X | C57BL/6J (N5) | Isolation-induced resident aggression | Suppressed | | D'Adamo et al. 2002 |
| Androgen receptor[3] | AR | X | C57BL/6 and 129SvEv | Isolation-induced resident aggression | Suppressed[2] | | Raskin et al. 2009 |

[+/−]: Data obtained from heterozygote of knockout mouse

[1]Behavioral change only at the first encounter

[2]Behavior change after repeated exposure

[3]Nestine-Cre-LoxP conditional knockout mice that selectively lack AR expression in the nervous system.

## Table 4

**Modulation of aggressive behaviors after local infusion of drugs targeting 5-HT receptors in selected brain regions**

| Brain Region | Type of Aggression, Species | Target; Drugs and Doses | Pharmacological Effects | References |
|---|---|---|---|---|
| **DRN** | Resident aggression, male rats | 5-$HT_{1A}$: 8-OH-DPAT, 1-10 μg. 5-$HT_{1A}$/5-$HT_{1B}$: Eltopronazine, 1-30 μg (agonists) | ↓ aggressive behavior, with inactivity and decreased social interaction | Mos et al. 1993 |
| | Resident aggression, male rats | 5-$HT_{1A}$: Alnespirone, 25 μg (agonist) | ↓ aggression; no side effects | Van der Vegt et al. 2003 |
| | Alcohol-escalated aggression, male mice | 5-$HT_{1A}$: 8-OH-DPAT, 1.0 μg 5-$HT_{1B}$: CP-94253, 1.0 μg (agonists) | 8-OH-DPAT and CP-94253: ↓ baseline aggression, with reduced motor activity; no effects on alcoho-lrelated aggression | Faccidomo et al. 2008 |
| | Schedule-heightened aggression, male mice | 5-$HT_{1B}$: CP-93129, 0.1-1.0 μg (agonist) | ↓ escalated aggression; reduced walking behavior | Bannai et al. 2007 |
| | Alcohol-escalated aggression, male mice | 5-$HT_{1B}$: CP-93129, 0.1-1.0 μg (agonist) | ↓ baseline and alcohol-related aggression (0.5-1.0 μg); concomitant reduction in motor activity | Faccidomo et al. submitted |
| | Maternal aggression, rats | 5-$HT_{1A}$: 8-OH-DPAT, 0.56 μg (agonist) | ↑ maternal aggression (0.56 μg); no motor effects DPAT-escalated aggression prevented by infusion of CP-93129 (1.0 μg) into the orbitofrontal cortex | Veiga et al. 2010 |
| **MRN** | Maternal aggression, rats | 5-$HT_{1A}$: 8-OH-DPAT, 0.2-2.0 μg (agonist) | ↓ maternal aggression; no side effects | De Almeida and Lucion, 1997 |
| **PAG** | Maternal aggression, rats | *Dorsal PAG* 5-$HT_{1A}$: 8-OH-DPAT, 0.2-2.0 μg (agonist) | ↓ maternal aggression (0.2-2.0 μg); no side effects | de Almeida and Lucion, 1997 |
| | Maternal aggression, rats | *Dorsal PAG* 5-$HT_{2A/2C}$: α-methyl-5-HT maleate, 0.2-1.0 μg (agonist) 5-$HT_{2A/2C}$: ketanserin, 1.0 μg (antagonist) | α-methyl-5-HT maleate: ↓ maternal aggression; no motor effects Ketanserin: no effects on aggression, decreased motor activity | de Almeida et al. 2005 |
| | Hypothalamic-stimulated defensive aggression, cats | *PAG* 5-$HT_{1A}$: 8-OH-DPAT*, 0.016 ng -1.0 μg 5-$HT_{2C}$: DOI*, 3.57 ng–0.54 μg (agonists) | 8-OH-DPAT: ↓ defensive hissing (0.66 – 1.0 μg), effect prevented by antagonist p-MPPI. No motor effect DOI: facilitation of defensive hissing (0.54 μg) | Shaikh et al. 1997 |
| **Septal nuclei** | Maternal aggression, rats | *Medial septal nucleus* 5-$HT_{1A}$: 8-OH-DPAT, 0.2-2.0 μg (agonist) | ↑ maternal aggression (0.2-0.5 μg); reduced activity only with highest dose (2.0 μg) | de Almeida and Lucion, 1997 |
| | Maternal aggression, rats | *Medial septal nucleus* 5-HT2A/2C: alpha-methyl-5-HT maleate, 0.2-1.0 μg (agonist) 5-HT2A/2C: ketanserin, 1.0 μg (antagonist) | No effects on aggressive or non-aggressive behaviors (agonist) Ketanserin: no effects on aggression, but decreased motor activity | de Almeida et al. 2005 |

DRN = dorsal raphé nucleus; MRN = median raphé nucleus; PAG = periaqueductal gray area;

*doses calculated based on the following molecular weights (MW) of the compounds (as available at Sigma-Aldrich): 8-OH-DPAT hydrobromide, MW=328.29; CGS-12066 maleate salt, MW=450.41; DOI hydrochloride, MW=357.62.