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Behavioral and Pharmacogenetics of Aggressive Behavior

Aki Takahashi¹, Isabel M. Quadros², Rosa M. M. de Almeida³, and Klaus A. Miczek⁴

¹Mouse Genomics Resource Laboratory, National Institute of Genetics (NIG), Mishima, Shizuoka, Japan

²UNIFESP, Vila Clementino, SP, Brazil

³UFRGS, Porto Alegre, RS, Brazil

⁴Departments of Psychology, Psychiatry, Pharmacology and Neuroscience, Tufts University, Medford and Boston, Massachusetts, USA

Abstract

Serotonin (5-HT) has long been considered as a key transmitter in the neurocircuitry controlling aggression. Impaired regulation of each subtype of 5-HT receptor, 5-HT transporter, synthetic and metabolic enzymes has been linked particularly to impulsive aggression. The current summary focuses mostly on recent findings from pharmacological and genetic studies. The pharmacological treatments and genetic manipulations or polymorphisms of a specific target (e.g., 5-HT_{1A} receptor) can often result in inconsistent results on aggression, due to “phasic” effects of pharmacological agents vs “trait”-like effects of genetic manipulations. Also, the local administration of a drug using the intracranial microinjection technique has shown that activation of specific subtypes of 5-HT receptors (5-HT_{1A} and 5-HT_{1B}) in mesocorticolimbic areas can reduce species-typical and other aggressive behaviors, but the same receptors in the medial prefrontal cortex or septal area promote escalated forms of aggression. Thus, there are receptor populations in specific brain regions that preferentially modulate specific types of aggression. Genetic studies have shown important gene × environment interactions; it is likely that the polymorphisms in the genes of 5-HT transporters (e.g., MAO A) or rate-limiting synthetic and metabolic enzymes of 5-HT determine the vulnerability to adverse environmental factors that escalate aggression. We also discuss the interaction between the 5-HT system and other systems. Modulation of 5-HT neurons in the dorsal raphe nucleus by GABA, glutamate, and CRF profoundly regulate aggressive behaviors. Also, interactions of the 5-HT system with other neuropeptides (arginine vasopressin, oxytocin, neuropeptide Y, opioid) have emerged as important neurobiological determinants of aggression. Studies of aggression in genetically modified mice 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. BDNF, nNOS, αCaMKII, Neuropeptide Y). The future agenda delineates specific receptor subpopulations for GABA, glutamate and neuropeptides as they modulate the canonical aminergic neurotransmitters in brainstem, limbic and cortical regions with the ultimate outcome of attenuating or escalating aggressive behavior.

1. Introduction

One of the oldest roots of the neurogenetic analysis of aggressive behavior can be traced to the domestication of feral animals, as illustrated experimentally in the elevated brain levels of serotonin in tame silver foxes (e.g., Popova et al. 1991). No other transmitter system has been more consistently implicated in the neurobiological mechanisms mediating impulsive aggressive behavior than serotonin (Miczek et al. 2002; Miczek et al. 2007; Takahashi et al. 2011). Serotonin emerged as the focus in the initial phase of “top-down” genetics of aggressive behavior, when the brains of individuals that were selected for high aggressive traits revealed lower levels of serotonin, its major acidic metabolite and some of the receptor or transporter molecules upon which this amine acts (Brown et al. 1979; Garattini et al. 1967; Linnoila et al. 1983). It continues to be the key transmitter system of interest in the more recent phase of “bottom-up” genetics, when the gene for a specific receptor or transporter was deleted and the behavioral phenotype indicated a higher than normal level of aggressive behavior (Bouwknicht et al. 2001a; Saudou et al. 1994).

The current understanding of serotonergic mechanisms in aggressive behavior has to accommodate two different but interacting sources of influence. Classically, serotonin has been studied for its role in the predisposition to engage in impulsive violent and anti-social behavior. The question of interest continues to be which features of serotonergic transmission – its rate of synthesis, uptake, metabolism, receptor and transporter expression – are characteristic of an aggressive heritable trait that runs in families (Brunner et al. 1993a). It has become clear that the seductively simple serotonin deficiency hypothesis that links low serotonin activity to the propensity for aggressive behavior is being replaced by more sophisticated and detailed schemes. Recent clinical and preclinical data point to important allelic differences in the genes for specific serotonin receptor subtypes, transporter molecules and metabolic enzymes in impulsively aggressive individuals (de Boer and Koolhaas 2005; Lesch and Merschdorf 2000; Miczek et al. 2002; Miczek et al. 2007; Nelson and Chiavegatto 2001; Takahashi et al. 2011).

A second role for serotonin is to modulate aggressive behavior by its phasic activity, particularly during the anticipation of aggressive and defensive acts and at the termination of an aggressive bout. Superimposed on the serotonergic tone are transient changes in release, impulse flow and receptor activation that are synchronized with the initiation and termination of bouts of aggressive and defensive acts (Ferrari et al. 2003). Phasic serotonergic activity appears to be linked to bouts of several species-normative consummatory behaviors ranging from feeding, drinking, and sexual acts to fighting, and to pathological excesses of these activities. Neuroplastic changes in serotonergic pathways from the dorsal raphe neurons to the neo- and paleocortical terminals result from repeated aggressive experiences as reflected in serotonin receptor regulation, firing rate and release. To further our understanding of the interaction between tonic and phasic serotonergic activities ideally requires real-time measurements over the course of a circadian cycle and arranging conditions that provide a challenge behaviorally and neurochemically.

During the last decade, epigenetic mechanisms for the expression of certain genes that encode for serotonergic metabolic enzymes, transporter proteins and receptors have been

scrutinized for their role in impulsively violent individuals. Stressful experiences such as abusive maltreatment during a critical developmental period can lead young adults to engage in more impulsive and violent behavior, particularly in those individuals who are characterized by the expression of a certain allelic variety of Monoamine Oxidase A, an important metabolic enzyme for serotonin (Caspi et al. 2002).

The last decade has seen also a concerted effort to translate more readily between preclinical data and clinical observations, and vice versa. This is evident from both an increasing focus on escalated, atypical forms of aggressive behavior in animal models, and by efforts to define aggressive behaviors using operational and functional definitions and assessments in clinical settings (DSM V).

2. Definition and Measurement of Aggression

Most research on the neurogenetics of serotonin and aggression in both human and veterinary medicine seeks to understand and control pathological aggression (Volavka et al. 2005), while laboratory experiments using animal models typically deal with adaptive, species-typical aggressive behavior. When studying aggression in animals, it is important to consider the ethological significance of the behavior, including its phylogenetic and ontogenetic development and the functions it serves for individuals and the species. Aggressive signals, postures and acts are used to help an animal obtain specific goals, or to defend against threats actual attacks (Miczek et al. 2002). These behaviors occur when individuals compete for food, water and other resources necessary for survival and reproduction (resident-intruder aggression), when they defend their territory or offspring (territorial and maternal aggression), or in response to frustration or fear (Miczek et al. 2001). Engaging in aggressive behavior is often beneficial to the individual and the species. For example, dominance hierarchies are established and maintained through confrontations between rival males (Figure 1), and so-called isolation-induced aggression mimics many elements of the behavior used by resident males to exclude other breeding males from their home territory and their mates (Brain and Benton 1979; Miczek et al. 2001; Table 1). However, it should be noted that isolated housing results in social avoidance in a large proportion of a sample of mice, while aggressive behavior is seen in varying numbers of isolated animals depending on species and strain.

Aggressive behavior can be classified as offensive or defensive based upon the distal and proximal conditions that precipitated it, the topography of the behavior, and its consequences (Blanchard and Blanchard 1977; Brain 1979). Defensive behaviors occur in response to threatening or fear-inducing stimuli and often result in escapes (Brain 1979). In male rodents, specific defensive behaviors include escape, freezing, defensive postures and threats, which occur in response to attacks by either predators or conspecifics (Blanchard et al. 2003; Pellis and Pellis 1988; Rasia-Filho et al. 2008). Postpartum female rodents engage in maternal aggression, which includes both defensive and offensive elements, to protect their newborn offspring from male intruders (Lucion and de Almeida 1996; Parmigiani et al. 1998).

“Violence” is a controversial concept among ethologists. The term has been used to describe escalated, pathological and abnormal forms of aggression characterized by prolonged and frequent attack bites and aggressive behavior with brief latencies (Miczek et al. 2002; Miczek et al. 2003). The differences are quantitative rather than qualitative, with violence marked by shorter attack latencies and higher frequencies and longer durations of fighting than adaptive aggression. Violence has been described to be qualitatively different from adaptive aggression. For instance, attack bites aimed at vulnerable parts of the opponent’s body are considered abnormally aggressive, when adaptive aggression consists of less-injurious bites directed at the intruder’s back and flanks (Haller et al. 2005). Additional qualitative distinctions that have been proposed include context-independent attacks, which are directed at an opponent regardless of its sex, responsiveness (free-living/anaesthetized/dead) or the test environment (home/neutral cage) (Koolhaas 1978), and lack of ritualistic behaviors, quantified as Attack/Threat (A/T) ratios (Haller et al. 2005). Therefore in principle “violence” could refer either to quantitatively escalated or hyper-aggression, or to qualitatively abnormal forms of aggression, or even rarely to aggression that is both escalated and abnormal (for review see Natarajan and Caramaschi 2010).

Human and non-human aggressive behaviors have some common features, but most animal aggression is less complex. Social norms establish boundaries for what is accepted as appropriate aggressive behavior, but the array of inappropriate interpersonal behaviors classified as violence is a serious social and mental health issue (Ferris et al. 2008). Numerous psychiatric disorders defined in the DSM-IV R and the new DSM-V (scheduled for publication in May 2013), including schizophrenia, brief reactive psychosis, anxiety disorder, adjustment disorder, impulse control disorder, antisocial personality disorder, attention deficit disorder, mania/depression, PTSD, autism, and substance abuse, specify aggressive behavior among their symptoms (Boles and Miotto 2003; Raine 2002; Rydén et al. 2009; Volavka et al. 2005).

It can be useful to classify human aggressive behavior as either defensive, premeditated, or impulsive-hostile in nature (Stoff and Vitiello 1996; Vitiello and Stoff 1997). The premeditated (e.g., predatory and instrumental) and impulsive forms of aggression are especially likely to be diagnosed as pathological and in need of treatment. Impulsive, but not premeditated, aggression is linked to biological and environmental causes, as well as pharmacological or psychological treatment response factors, by a growing body of empirical data (Coccaro et al. 2010).

Aggression as a behavioral state in humans has usually been measured by provoking subjects in competitive situations with fictitious opponents and then giving them opportunities to engage in quantifiable responses that are defined as aggressive (see Table 2, for review see Miczek et al. 2002). Human aggression as a trait is assessed using psychometric measures including inventories, questionnaires and scales. The role of 5-HT in human aggression has been successfully investigated using such laboratory techniques (Table 2), but relating laboratory indices of aggression to actual violence and aggression outside the laboratory remains a critical challenge for such approaches; identifying subtypes of human aggression with psychometric and laboratory methods is also difficult. The psychometric instruments used to differentiate between individuals with contrasting

aggressive traits such as the impulsive – reactive – hostile – affective subtype versus the controlled – proactive – instrumental – predatory subtype (Stoff and Vitiello 1996) are summarized in Table 2.

3. Aggressive “trait” vs. “states”

A frequently reiterated theory, based on early clinical and preclinical studies, links impulsive, hostile, and violent behavior to a serotonin deficiency (Brown and Goodwin 1986; Goldman et al. 1992; Lesch and Merschdorf 2000; Linnoila and Virkkunen 1992; Mann 1999; Valzelli 1977). Individuals exhibiting such behavior may benefit from pharmacological treatments aimed at inhibiting 5-HT transporters (e.g., SSRIs such as fluoxetine or citalopram), activating 5-HT_{1A} receptors (e.g., buspirone) or blocking 5-HT_{2A} receptors (e.g., risperidone). Acute treatment with these drugs induces phasic changes in 5-HT function that are associated with their transient anti-aggressive effects. In vivo microdialysis allows transient changes in extracellular 5-HT levels to be monitored in anticipation of, during, and after aggressive encounters in rats. One study reported reduced 5-HT levels in the prefrontal cortex during and after the aggressive confrontation, while no changes were detected in the nucleus accumbens, another terminal region (Van Erp and Miczek 2000; Figure 2). By contrast, chronic treatment with these anti-aggressive compounds may promote as yet undefined neuroadaptive changes in 5-HT function such as autoreceptor desensitization, which may in turn be associated with the emergence of therapeutic effects.

On the other hand, aggression as a “trait” is the focus of genetic studies. While these aggressive traits are clearly polygenic, it is remarkable that several studies have found an interaction between genotypes such as TPH2, MAO-A and 5-HTT polymorphisms and environmental triggers such as social stress underlying an increased likelihood of violent outbursts (see below). For example, a SNP in TPH2 gene (A2051C) has been linked to aggressive behavior in rhesus monkeys. Monkeys with the AA/AC genotype that were reared without their mother (peer-reared) showed increased aggressive acts compared to those with a CC genotype, but the difference disappeared when infants of both genotypes were reared by their mothers (Chen et al. 2010). This review will focus on the interaction between salient environmental events and genes and the subsequent effects on aggressive behaviors.

Gene-gene interactions are also of interest and need to be explored. For example, Passamonti et al. (Passamonti et al. 2008) showed interactions between 5-HTT and MAOA polymorphisms that affected the activity of the anterior cingulate cortex, a brain area that has been implicated in impulsivity, including impulsive aggression. Many other genes may have subtle effects on aggressive phenotypes, and stronger effects may emerge as a result of complex epistatic interactions between those genes (Miczek et al. 2001). In the past 15 years, most rodent studies on genetics and aggressive behavior have used conventional knockout techniques, in which the expression of a gene is completely deleted, affecting the whole body through all developmental stages and inducing compensatory changes in other genes (trait-like change; see Table 3). Newer, more subtle methods, including conditional knockout, viral vector microinfusion, and drug-inducible knockout techniques, can produce

transient and local changes in gene expression, allowing the study of more “phasic” changes in gene expression and how they influence aggression. Such studies may explain some of the discrepancies in the results from previous genetic and pharmacological studies of 5-HT function and aggression.

4. 5-HT receptors

Considerable evidence suggests that serotonin receptors regulate aggressive behaviors in various animal species. Among the multiple 5-HT receptor subtypes, it is mainly the first two families of serotonin receptors (5-HT₁ and 5-HT₂) which have been studied in regard to their role on aggression (Miczek et al. 2002; Olivier 2004). There is some, but less, information on the involvement of 5-HT₃ receptors on aggressive behaviors (McKenzie-Quirk et al. 2005; Ricci et al. 2004; Rudissaar et al. 1999). Further development of adequate pharmacological tools that can activate or inhibit a certain subtype of 5-HT receptor specifically is required to study the role of other receptor subtypes (e.g., 5-HT₅, 6, 7, 1e, 1f) on aggression.

4-1. 5-HT₁ family

Pharmacological approach—The 5-HT_{1A} receptor partial agonist buspirone has been used clinically to reduce general anxiety. It was shown that buspirone also reduces aggressive behavior in mentally retarded patients (Kavoussi et al. 1997; Ratey et al. 1991), and 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). Similar findings have been reported in preclinical studies; systemic administration of 5-HT_{1A} receptor agonists (e.g. 8-OH-DPAT, repinotan, alnespirone) dose-dependently decrease aggressive behaviors in a wide range of animal species, including fish, amphibians, 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 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). One exception are fruit flies (*Drosophila melanogaster*), as they showed increased aggressive behavior after 8-OH-DPAT treatment (Johnson et al. 2009). Selective antagonists of 5-HT_{1A} receptors such as WAY-100635 successfully reversed the effect of 5-HT_{1A} agonists, while the administration of the antagonist by itself did not show any effect on aggression (de Boer and Koolhaas 2005; Mendoza et al. 1999; Miczek et al. 1998b). Notably, in laboratory studies the anti-aggressive effects of most of 5-HT_{1A} agonists are accompanied by nonspecific behavioral side effects including sedation, motor inactivity, 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 (i.e., alnespirone and S-15535) reduced aggressive behavior specifically without changing the other non-aggressive behaviors, at least in a wild-derived rat strain (de Boer et al. 1999; de Boer et al. 2000; de Boer and Koolhaas 2005). These compounds are suggested to have different effects on 5-HT receptors on presynaptic and postsynaptic terminals (de Boer and Koolhaas 2005), and thus

it is possible that a subpopulation of 5-HT_{1A} receptors on which those compounds acts is involved in anti-aggressive effect specifically.

The 5-HT_{1B} receptor agonists seem more specific in their anti-aggressive effect than 5-HT_{1A} agonists. In mice and rats, the systemic administration of 5-HT_{1B} agonists (e.g. CP-94253, CP-93129, CGS-12066B) reduces aggressive behavior without sedation, or motor or sensory impairment (de Almeida et al. 2001a; de Almeida and Miczek 2002; de Boer and Koolhaas 2005; Fish et al. 1999; Miczek et al. 2002; Miczek et al. 2004; Mos et al. 1993; Olivier et al. 1990; Olivier 2004; Figure 3). These effects were antagonized by 5-HT_{1B/1D} antagonist GR-127935, further confirming that the anti-aggressive effects of these compounds were mediated by 5-HT_{1B} receptors (de Boer and Koolhaas 2005). However, there are no clinically approved drugs that target 5-HT_{1B} receptors. There is an amino acid difference in the binding domain of 5-HT_{1B} receptors of humans and rodents, and therefore the pharmacological sensitivity and specificity of 5-HT_{1B} agonists in rodents may not compare with those in humans (Olivier 2004).

The precise functions and sites of action for the anti-aggressive effects of 5-HT_{1A} and 5-HT_{1B} receptors still remain to be resolved. One site of inhibitory action for 5-HT is the 5-HT₁ autoreceptors that are localized at either the somata or the synaptic terminal of serotonin neurons. Stimulation of 5-HT₁ autoreceptors inhibits serotonergic neural activities and therefore reduces 5-HT impulse flow and release. On the other hand, 5-HT₁ receptors are also localized at the postsynaptic terminal as heteroreceptors at the projection sites of serotonin neurons. By contrast, the effect of agonists that act on 5-HT₁ heteroreceptors can be interpreted as increasing 5-HT neurotransmission.

Microdialysis studies have shown that both systemic and intra-raphé administration of 5-HT_{1A} and 5-HT_{1B} agonists decreased extracellular levels of 5-HT in the forebrain areas including striatum, hippocampus and frontal cortex (Adell et al. 2001; Bonvento et al. 1992; De Groote et al. 2003; Dekeyne et al. 2000; Gobert et al. 1998; Hjorth and Sharp 1991; Johnson et al. 2001; Knobelmann et al. 2000; Kreiss and Lucki 1994; Sprouse and Aghajanian 1987). These data suggest that the inhibition of 5-HT release by 5-HT_{1A} and 5-HT_{1B} agonists is mediated by the 5-HT₁ autoreceptors. Note that these findings suggest that compounds which decrease 5-HT neurotransmission concurrently reduce aggressive behavior, which challenges the serotonin deficiency hypothesis of aggression.

On the other hand, the importance of the 5-HT_{1A} and 5-HT_{1B} heteroreceptors on projection sites has been emphasized in studies using lesion or depletion of raphé 5-HT neurons either by systemic administration of the tryptophan hydroxylase inhibitor PCPA or by intracerebral injection of the 5-HT neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT). Since these neurotoxic treatments destroy the function of serotonergic neurons, one can observe the effect of 5-HT₁ agonists on postsynaptic receptors exclusively. If only somatodendritic and presynaptic autoreceptors are the site of action of 5-HT_{1A} and 5-HT_{1B} agonists, PCPA or 5,7-DHT treatment should eliminate the anti-aggressive effect of 5-HT_{1A} and 5-HT_{1B} agonists. However, lesions or depletion of 5-HT neurons did not affect the anti-aggressive effects of 5-HT_{1A} and 5-HT_{1B} agonists (de Almeida et al. 2001b; Miczek et al. 1998b) or even had pro-aggressive effects (Sanchez and Hyttel 1994; Sijbesma et al. 1991). While

these data may suggest postsynaptic 5-HT₁ receptors as critical sites of action, it is important to note that these pharmacological depletions spared a subpopulation of receptors.

The intracranial microinjection technique has been used to determine the critical brain regions underlying the anti-aggressive effects of 5-HT_{1A} and 5-HT_{1B} receptor agonists (Table 4). 5-HT in the mammalian central nervous system derives mainly from the dorsal and median raphe nuclei (DRN and MRN, respectively). Activation of 5-HT_{1A} and 5-HT_{1B} receptors in the 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 MRN also reduced aggressive behavior of lactating female rats (de Almeida and Lucion 1997). 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, periaqueductal gray) reduced aggressive behavior in various procedures and species (see Table 4). Interestingly, under conditions that may escalate aggression, such as consumption of moderate doses of alcohol or maternal aggression, a 5-HT_{1A} or 5-HT_{1B} 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.

Genetic approach—The 5-HT_{1B} receptor was the first molecule to be linked to aggression by using the gene knockout technique. Male mice with disrupted 5-HT_{1B} receptor expression (*Htr1b*^{-/-}) increased isolation-induced aggressive behavior compared to the wild-type mice (Bouwknicht et al. 2001b; Saudou et al. 1994). However, aggressive behavior of the background strain of mice (129/Sv-ter) was very low, close to zero, and thus the frequency of attack bites in *Htr1b*^{-/-} was low and the latency to initiate fighting 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 (Bouwknicht et al. 2001a). Females of *Htr1b*^{-/-} increased their aggressive behavior during the postpartum period (Brunner and Hen 1997). These results suggest a role for 5-HT_{1B} receptors in the inhibition of some aggressive and impulsive behaviors. The level of tissue 5-HT concentration in *Htr1b*^{-/-} mice was lower than wild-type in nucleus accumbens and spinal cord (Ase et al. 2000).

There are several polymorphisms in the human 5-HT_{1B} receptor (*HTR1B*) gene. The most frequently studied *HTR1B* polymorphism in relation to aggressive phenotype is a single nucleotide polymorphism (SNP) G861C. This SNP had significant linkage with aggressive behavior in antisocial alcoholism (Lappalainen et al. 1998). Specifically, 861C, the SNP with lower 5-HT_{1B} receptor expression (Huang et al. 1999), was related to antisocial behavior. This SNP is actually a synonymous polymorphism, in which no amino-acid

change occurred, and thus this SNP seems not to have any function by itself. Thus, G861C polymorphism may have a linkage with other functional polymorphisms that causes the expression change of 5-HT_{1B} receptors. Jensen et al. (2009) showed that a SNP (A1997G) in a non-coding regulatory region of the HTR1B gene is actually related to the 5-HT_{1B} expression pattern. This SNP is in the binding site for the microRNA miR-96 that inhibits the translation or degrades the HTR1B mRNA. College students homozygous for the A-allele, who have reduced 5-HT_{1B} receptor expression, reported a greater history of aggressive behaviors than G-allele individuals. Also, another SNP in the 5'UTR region of the HTR1B gene, A161T, was found to correlate significantly with a history of aggression in subjects who completed violent suicides (Zouk et al. 2007). Individuals with the T161 locus had more lifetime aggressive behaviors, and again this polymorphism was linked to reduced transcriptional activity of 5-HT_{1B} receptors (Sun et al. 2002). However, these associations between the HTR1B polymorphisms (G861C, G261T, or C129T) and aggression and antisocial behavior are not seen in other studies (Huang et al. 1999; Kranzler et al. 2002; New et al. 2001; Sinha et al. 2003; Van den Berg et al. 2008). Based on the findings from pharmacological studies and gene knockout and polymorphism studies, it is likely that the 5-HT_{1B} receptor has an important role in the inhibition of certain types of aggression.

In contrast to the strong pharmacological evidence implicating the 5-HT_{1A} receptor in aggression, no linkage has yet been reported between the 5-HT_{1A} gene polymorphism and aggression. Also, deletion of 5-HT_{1A} gene (Htr1a^{-/-}) reduced aggressive behavior in mice (Zhuang et al. 1999), which is the complete opposite of the findings with 5-HT_{1A} agonists. 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, mice selected for short latency to attack showed higher 5-HT_{1A} receptor expression and receptor sensitivity (Korte et al. 1996; Van Der Vegt et al. 2001; van Riel et al. 2002; Veenema et al. 2005), while 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.

4-2. 5-HT2 family

Pharmacological approach—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). However, some reports cast doubt on the routine use of antipsychotics (Swanson et al. 2008; Tyrer et al. 2008). In one study, the placebo control group showed the greatest reduction in aggressively challenging behavior compared to antipsychotic drug treatments in people with intellectual disability (Tyrer et al. 2008). In animal models, selective 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 reduces 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 anti-aggressive effects of 5-HT₂ ligands are accompanied by sedative effects in the same dose range. Local infusion of a 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-HT₂ receptor subtypes, and promises to dissociate the anti-aggressive and sedative effects.

Genetic approach—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). Positive correlation between impulsive physical aggression and 5-HT_{2A} receptor expressions in orbitofrontal cortex has been reported using PET (Rosell et al. 2010) and a similar finding was reported in a postmortem study of suicide victims (Mann et al. 1986; Oquendo et al. 2006). However, another PET study reported opposite changes in 5-HT_{2A} receptor expression (Meyer et al. 2008). 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, a significant linkage was found between polymorphisms in the 5-HT_{2A} receptor (HTR2A) gene, 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 HTR2A polymorphisms (Khait et al. 2005; Van den Berg et al. 2008). Again, the successful 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 HTR2A polymorphisms.

Linkage of a minor polymorphism in the 5-HT_{2B} receptor (HTR2B) gene with antisocial behavior was reported recently. The HTR2B Q20* allele, which is found exclusively in the Finnish population, contains a stop codon in HTR2B and blocked the expression of the 5-HT_{2B} receptor. Males with the Q20* allele are prone to show more impulsive violence or impulsive suicidal behavior interacting strongly with alcohol than control (Bevilacqua et al. 2010). Male mice with disrupted 5-HT_{2B} receptors (Ht2b^{-/-}) also showed increased impulsive behavior. Interestingly, these mice had three times higher testosterone level in the cerebrospinal fluid, which is also consisted with the Q20* individuals among humans.

5. Serotonin transporter (5-HTT)

Pharmacological approach

Aggressive behavior in humans and animals can be reduced and prevented by blocking serotonin transporter molecules, which in turn presumably increases 5-HT levels in the brain. Clinically, chronic treatment (i.e. >3 weeks) with selective serotonin reuptake

inhibitors (SSRIs) has been shown to reduce 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). However, SSRIs have occasionally been reported to increase the incidence of aggressive and suicidal behavior, and the causes of these paradoxical effects remain unknown (Spigset 1999; Troisi et al. 1995).

Both acute and chronic SSRI treatment can produce a dose-dependent reduction in aggressive behavior in animal models (Carrillo et al. 2009; Delville et al. 1996; Olivier et al. 1989; Pinna et al. 2003). When given acutely to rodents and non-human primates, several SSRIs including fluoxetine, fluvoxamine and sertraline reduced aggression in various contexts (Abbadie et al. 1994; 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). Mice treated with the SSRI citalopram daily for three weeks no longer showed increased levels of aggression after consuming a moderate dose of alcohol, and baseline levels of aggression also showed modest reductions (Caldwell and Miczek 2008). On the other hand, the very low levels of agonistic behavior typically seen in laboratory rats may be restored to species-typical levels by chronic SSRI treatment (Mitchell et al. 1991; Mitchell 2005; Mitchell and Redfern 1992; Mitchell and Redfern 1997). Thus, SSRIs are more likely to exhibit anti-aggressive effects in conditions of escalated agonistic behavior, such as fighting enhanced by alcohol (Caldwell and Miczek 2008).

Mechanistically, extracellular levels of 5-HT in the prefrontal cortex of rats are elevated by both acute and chronic administration of citalopram or the more potent isomer escitalopram, implying that SSRIs' effects on aggression and other mood disorders is a result of increased cortical 5-HT (Ceglia et al. 2004). However, the anti-aggressive effects of fluoxetine, another SSRI, may be mediated primarily by acting on neurosteroids and GABA transmission, and only secondarily by elevating 5-HT (Pinna et al. 2003; Pinna et al. 2006). In addition, long-term SSRI treatment probably recruits both pre- and post-synaptic mechanisms and neuroplastic events that may also have therapeutic actions (Benmansour et al. 1999; Blier and de Montigny 1998; Ceglia et al. 2004; Pineyro et al. 1994).

Genetic approach

The serotonin-transporter-gene-linked polymorphic region (5-HTTLPR) is a variation in the length of the 5'-flanking transcriptional control region (promoter) of the 5-HTT gene that affects the gene's transcriptional activity. The variation has been found in humans (Heils et al. 1996) and also in great apes and rhesus monkeys (Lesch et al. 1997). The short-length (*s*) allele reduces 5-HTT expression in vitro compared to the long length homozygote (*l/l*) and lowers the prolactin response to clomipramine in humans, indicating reduced 5-HT function (Heils et al. 1995; Lesch et al. 1996; Whale et al. 2000). Studies in humans have found that males and females with one or two copies of the *s* allele (*s/s*, *s/l*) exhibit more hostility, aggression, anxiety and depression and lower agreeableness than *l/l* homozygotes (Lesch and Merschdorf 2000). "Type 2" alcoholics who displayed high impulsivity and antisocial behaviors showed a higher frequency of the *s* allele than either "Type 1" alcoholics without antisocial behavior or healthy controls (Hallikainen et al. 1999). As in humans, rhesus

monkeys with the *s* allele were more aggressive than *l/l* individuals (Jarrell et al. 2008; Lesch and Merschdorf 2000).

5-HTT polymorphism also exhibits a genotype-environment interaction. Rhesus monkeys with the *s* allele that were peer-reared without their mothers had lower CSF levels of 5-hydroxyindoleacetic acid (5HIAA) than *l/l* individuals, but this difference was not present in maternally reared monkeys (Bennett et al. 2002). Peer-reared male monkeys also showed both altered CSF 5HIAA levels and an increase in aggression-related behavior (Higley et al. 1991; Kraemer et al. 1989). Humans carrying the *s* allele exhibited more suicidal ideations or attempts in response to stressful life events than *l/l* homozygotes, but did not differ in less stressful situations (Caspi et al. 2003). Therefore, it is possible that animals with the *s* allele are more vulnerable to stressful challenges, and subsequently escalate their aggressive behaviors towards others and themselves. However, the presence of the *s* allele did not affect human aggression consistently across sexes (Cadoret et al. 2003) or cultures (Baca-Garcia et al. 2004).

Deletion of the 5-HTT gene in mice (*Slc6a4*) produced seemingly contrary results. Wild-type C57BL/6J mice attacked more and showed shorter latencies to start fighting in the resident-intruder test than homozygote and heterozygote 5-HTT knockouts (Holmes et al. 2002; Table 3). 5-HTT knockout mice have higher extracellular 5-HT concentrations and lower 5-HT uptake in the forebrain compared to wild type (Mathews 2004). Knockout mice with reduced or absent 5-HTT function also exhibited more than 50 phenotypic changes, including alterations of behavioral, physiological, morphological, and sensory functions (Murphy and Lesch 2008), and those pleiotropic changes in various other phenotypes may contribute to the reduction of aggression in these mice. Comparable findings on 5-HTT and aggression have also been reported in rats; 5-HTT knockout rats on a Wistar/Crl background showed reduced offensive behaviors and longer attack latencies compared to wild types (Homberg 2007). Thus genetic ablation of 5-HTT has consistently been shown to reduce aggressive behaviors in rodents.

6. Monoamine oxidase A (MAOA)

Pharmacological approach

Inhibition of MAO_A leads to a reduction in the oxidative metabolism of monoamines, presumably making 5-HT and other monoamines more available in the brain. Although the importance of MAO inhibitors as antidepressants was soon recognized, only a few studies have evaluated the effects of MAO inhibitors on aggression in preclinical models (Miczek 1987). Non-selective inhibitors of both MAO_A and MAO_B (e.g. phenelzine, isocarboxazid, tranylcypromine) produce acute anti-aggressive effects only at doses that also produce sedation and alter other non-aggressive behaviors (DaVanzo et al. 1966; Sofia 1969; Valzelli et al. 1967; Welch and Welch 1968). Non-selective MAO inhibitors or selective MAO_B inhibitors can be clinically useful for treating patients with personality disorders who exhibit suicidal tendencies and impulsive aggression, but the drugs also have a profile of undesirable side effects (Hollander 1999; Raj 2004).

Genetic approach

The gene for MAOA was the first to be identified as a possible determinant for pathological aggression in humans, and it has remained the focus of most genetic and epigenetic studies. A Dutch family with a syndrome of borderline mental retardation and dysregulated impulsive aggression was identified by Brunner and colleagues (Brunner et al. 1993b). Aggressive outbursts were seen in all affected males in the kindred, and some exhibited aberrant sexual behavior, attempted murder and arson. Linkage and sequence analyses identified one missense mutation in the MAOA gene on the $\times$ chromosome, so that MAOA function was completely disturbed; the affected males had more serotonin and lower levels of norepinephrine, dopamine, and 5-HT metabolites in their urine (Brunner et al. 1993a). MAOA is also an important factor in animal aggression. Aggressive behaviors (skin wounds among cage mates and briefer attack latency in the resident-intruder test) escalated in male mice with a disrupted MAOA gene on either C3H/He or 129Sv background compared to wild type mice (Cases et al. 1995; Scott et al. 2008). Mice with an MAOA deficiency also showed a large increase in 5-HT and norepinephrine and a slight elevation in dopamine in the brain and liver (Cases et al. 1995; Kim et al. 1997; Table 3); the behavioral changes in the MAOA-deficient mice are probably caused by this change in 5-HT function. Escalated aggression in MAOA mutant mice was blocked by 5-HT_{2A} receptor antagonists such as ketanserin and MDL100907 (Shih et al. 1999). Some of the behavioral and brain structural abnormalities in the MAOA-deficient mice were ameliorated when 5-HT was depleted by PCPA early in the developmental process (Cases et al. 1995; Cases et al. 1996).

MAOA expression can also be affected by variable-number tandem repeat (VNTR) polymorphism on the upstream region of the MAOA gene. The number of tandem repeats determines MAOA levels: 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 powerful interaction between MAOA genotype and environment on aggressive behavior has been reported (Caspi et al. 2002; Figure 4). Individuals with low MAOA expression (MAOA-L) polymorphisms who suffered from abuse, neglect, or traumatic life events in the first 15 years of their lives were more likely to have a history of adolescent conduct disorder, violence and criminal arrests, and also scored higher on aggressive disposition in a self-report questionnaire compared to MAOA-L individuals without abuse or trauma, or individuals with higher MAOA expression (MAOA-H) (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). The effect of MAOA genotype disappeared if all subjects were lumped together regardless of rearing environment (Fresan et al. 2007), and MAOA-H individuals sometimes reported higher aggression in interviews and on questionnaires (Manuck et al. 2000; Manuck et al. 2002). The finding that individuals with the MAOA-L allele are vulnerable to environmental factors, showing a high propensity to engage in aggressive behaviors when in a stressful environment, is consistent in males but not females (Sjoberg et al. 2007). Rhesus monkeys have a similar repeat length variation polymorphism in the MAOA gene (rhMAOA-LPR) which is also linked to aggression. Monkeys with a low-activity allele who were reared by their mother showed more aggressive behavior and attained higher dominance rank than monkeys with the low-activity allele who were peer-reared separately

from their parents (Newman et al. 2005). Higley and Suomi (1986) attributed this inhibition of aggression to increased fear and anxiety in peer-reared monkeys.

Substantial differences in both volume and activity of limbic system and neocortical areas between MAOA-L and MAOA-H individuals have been found in neuroimaging studies (see Buckholtz and Meyer-Lindenberg 2008 for a review). In healthy male human volunteers with the MAOA-L variant, fMRI showed smaller limbic and orbitofrontal volumes and higher activity in amygdala and hippocampus during aversive recall (Meyer-Lindenberg et al. 2006), which may be related to violent behavior. Lower MAOA activity in cortical and subcortical brain areas is associated with elevated aggression as measured by a self-report questionnaire, with no effect of MAOA polymorphism (Alia-Klein et al. 2008). These data show that the MAOA activity is one determinant of the propensity to aggression. The interaction between MAOA polymorphism and stressful social experiences is especially critical, since it can escalate aggression and can also change relevant brain structures.

7. Modulation of serotonergic activity by other systems

The 5-HT neurons in the raphe nuclei are modulated by other amines, acids, peptides and steroids (Adell et al. 2002). Several efforts have been 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. Especially, dorsal raphe nucleus (DRN), the largest 5-HT nucleus in the brain, will be highlighted because of its important role for aggression (Bannai et al. 2007; Faccidomo et al. 2008; Jacobs and Cohen 1976; Koprowska and Romaniuk 1997; Mos et al. 1993; Sijbesma et al. 1991; Van Der Veegt et al. 2003; Vergnes et al. 1986).

7-1 Excitatory and Inhibitory Amino acids

γ -Aminobutyric acid (GABA)—GABA is the major inhibitory neurotransmitter in the brain. Large numbers of GABA interneurons and distal GABAergic afferents are 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 vivo electrophysiology studies have shown that the activation of either GABA_A or GABA_B receptors can inhibit the cell firing of serotonergic neurons (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 5-HT release may be differentially modulated by GABA_A receptors and GABA_B receptors depending on the projection sites (Tao et al. 1996). In addition, microinjection of a GABA_B receptor agonist into the DRN can induce either increases or decreases of 5-HT neuronal activity (Abellan et al. 2000; Takahashi et al. 2010b; Tao et al. 1996).

Systemic administrations of positive modulators of GABA_A receptors such as benzodiazepines, barbiturates, and neurosteroids exert dose-dependent biphasic effects on aggressive behaviors, from escalation to inhibition (Miczek et al. 2003). Low to moderate doses of GABA_A positive modulators escalate aggression in mice, rats, pigs, and monkeys (Arnone and Dantzer 1980; Cole and Wolf 1970; Ferrari et al. 1997; Fish et al. 2001;

Gourley et al. 2005; Miczek 1974; Miczek and O'Donnell 1980; Mos and Olivier 1989; Rodgers and Waters 1985; Weerts and Miczek 1996). On the other hand, pharmacological activation of GABA_A receptors in the DRN inhibits aggressive behaviors in rats (Van Der Vegt et al. 2003) but has no effect in mice (Takahashi et al. 2010a). However, we found an interaction between alcohol and GABA_A receptor in the DRN on aggressive behavior. Only under the influence of alcohol, local administration of GABA_A receptor agonist muscimol in the DRN also heightened aggressive behaviors (Takahashi et al. 2010a). Therefore, GABA_A modulation of serotonergic neurons may connect to drug-induced escalated aggression (e.g., alcohol, benzodiazepines) but not to species-typical aggression.

GABA_B receptors in the DRN are also involved in the escalation of aggression in mice. Pharmacological activation of GABA_B receptors in the DRN escalates inter-male aggression (Takahashi et al. 2010b). The pro-aggressive effect of GABA_B agonist baclofen was blocked by selective agonists of GABA_B receptors (phaclofen, CGP54626). Additionally, the systemic administration of baclofen also escalates aggression in male mice. Therefore, both GABA_A and GABA_B receptors are involved in escalated aggression via different mechanism to modulate different types of aggression. *In vivo* microdialysis showed that GABA_B activation in the DRN increased extracellular 5-HT level in the medial prefrontal cortex (Takahashi et al. 2010b; Figure 5). This result suggests that the phasic activation of 5-HT system may be able to promote certain types of escalated aggressive behaviors in mice.

Glutamate—The DRN receives 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-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolopropionate/kainate (AMPA/kainate), ionotropic receptors for glutamate, 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). Metabotropic receptors of glutamate (mGluRs) are also found in the DRN, but their function on serotonergic neurotransmission and aggressive behavior needs to be characterized by further investigations. 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 marked side-effects (Belozertseva and Beshpalov 1999; Lang et al. 1995; Miczek and Haney 1994; Tyler and Miczek 1982). Memantine and neramoxane block the channel of NMDA receptors with different characteristics and promote alcohol-heightened aggression in resident mice confronting an intruder. Anatomically discrete analysis is required to identify the sites of action for NMDA receptors that produce escalated 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) is implicated in the emotion regulation including aggression (Davidson et al. 2000; Miczek et al. 2007). This mPFC-DRN glutamatergic

projection is involved in the controllability or emotion regulation (Amat et al. 2005) and it is possible that this pathway is also involved in the regulation of aggression.

7-2 Neuropeptides

Corticotropin-releasing factor (CRF)—The DRN is innervated by CRF immunoreactive fibers, and is the site for both subtypes of CRF receptors, CRF1 and CRF2 (Chalmers et al. 1995; Potter et al. 1994; Swanson et al. 1983). CRF, CRF receptors and other peptides of the CRF family (i.e. urocortins), play key modulatory roles on DRN 5-HT neurons (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).

CRF, CRF1 and CRF2 receptors are implicated in 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, i.c.v. or intra-amygdala infusions of low doses of CRF itself facilitated or induced pro-aggressive effects (Elkabir et al. 1990; Tazi et al. 1987). Under conditions of escalated aggression promoted by moderate doses of alcohol in male mice, CRF1 receptors are a promising target for pharmacological intervention. Systemic administration of the antagonists of CRF1 receptors reduce alcohol-heightened aggression, but also reduce baseline levels of aggressive behavior (Quadros et al. 2009b). When locally administered into the DRN, CRF1 antagonists (e.g., CP-154526 or MTIP) prevent the escalated levels of aggression observed after consumption of alcohol, with no detectable side effects on other behaviors. Remarkably, such anti-aggressive effects of CRF1 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 CRF2 antagonist (e.g., Astressin-2B) into the DRN escalates aggressive behavior (Quadros et al. 2009a).

The modulation of aggressive behaviors by CRF systems depends on the species such as mice or 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 escalated aggression that is promoted by alcohol, with presumably opposing roles for CRF1 and CRF2 receptors.

Neuropeptide Y (NPY)—NPY controls primarily food intake, energy balance, and metabolic regulation (Herzog 2003). In addition to the critical role for energy homeostasis, NPY is also implicated in aggressive behavior (Emeson and Morabito 2005). Male mice with deleted expression of Y1 receptor ($Y1^{-/-}$) showed obesity and reduced energy homeostasis (Kushi et al. 1998). These animals also exhibited increased aggressive behaviors in the resident-intruder test (Karl et al. 2004). However, escalated aggression was observed only in the home cage but not in the novel environment in $Y1^{-/-}$ mice. Both NPY and its receptors can be found in the DRN (Martel et al. 1990; O'Donohue et al. 1985; Saria

et al. 1984), and NPY inhibits both hyperpolarizing and depolarizing slow synaptic potentials in the DRN (Kombian and Colmers 1992). $Y1^{-/-}$ mice showed reduced expression of tryptophan hydroxylase mRNA in the raphe nuclei, and also 5-HT_{1A} agonists could suppress the heightened aggression of $Y1^{-/-}$ mice (Karl et al. 2004). These results suggest that the disruption of Y1 receptor expression specifically increases territorial aggression by altering 5-HT function.

Arginine vasopressin (AVP)—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 et al. 1992; Goodson 2008; Koolhaas et al. 1990; Neumann et al. 2010; Winslow and Insel 1993). Selective antagonists of vasopressin V1a receptors (SRX251, [d(CH₂)⁵Tyr(Me)AVP]) inhibited inter-male aggression (Ferris et al. 2006; Ferris and Potegal 1988), suggesting the involvement of V1a receptors in aggressive behaviors. Evidence points to a critical role of the interaction between AVP and 5-HT in 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 or lateral hypothalamus increased aggressive behavior in hamsters, and systemic fluoxetine, a 5-HTT inhibitor, blocked the pro-aggressive effect of AVP (Delville et al. 1996; Ferris et al. 1997). Therefore, 5-HT may have an inhibitory effect on the AVP-heightened aggression. By 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 over-activation of the dorsal 5-HT neurons and increased 5-HT concentration in the hypothalamus (Kim et al. 2009a). Further investigation will 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.

Oxytocin—Oxytocin, which has a structure similar to vasopressin, differing in only two amino acid positions, also plays an important role in the control of social behaviors like vasopressin. Administration of the agonists of oxytocin receptor increased aggressive behavior in lactating females (Bosch et al. 2005; Ferris et al. 1992) but reduced territorial aggression in males (Harmon et al. 2002). Mice in which the gene for oxytocin and its receptor were knocked out, showed enhanced aggressive behaviors in both males and lactating females (Ragnauth et al. 2005; Takayanagi et al. 2005; Winslow et al. 2000) but see (DeVries et al. 1997). In humans, the level of oxytocin in the CSF is inversely correlated with the life history of aggression (Lee et al. 2009). Oxytocin and its receptor are expressed in the DRN, and the effect of local infusion of oxytocin can facilitate passive avoidance in rats (Kovács et al. 1979). However, the exact interactions between the oxytocin and

serotonergic systems in their modulatory effects on aggressive behavior remain to be discovered.

7-3 Other molecules that directly or indirectly affect 5-HT pathways and aggression

Tryptophan hydroxylase (TPH)—Variations in TPH activity can directly affect 5-HT neurotransmission. Polymorphisms in the TPH1 or TPH2 gene change the enzyme activity and 5-HT level (Jonsson et al. 1997) for TPH1 gene; (Cichon et al. 2008; Lin et al. 2007; Zhang et al. 2004; Zhang et al. 2005) for TPH2 gene). Two SNPs in tight linkage disequilibrium, A218C and A779C, located in the intron of TPH1 gene (which are often referred to as U (upper) and L (lower) allele), have been shown to be associated with state and trait anger as assessed by interview and self report questionnaires (Manuck et al. 1999; Rujescu et al. 2002). Lower CSF 5-HIAA levels have been observed in healthy men, but not women, with the U allele (Jonsson et al. 1997), whereas the lowest CSF 5-HIAA was observed in LL carriers diagnosed with antisocial alcoholism (Nielsen et al. 1994). Apparently, both U and L alleles may relate to different types of aggression. Hennig et al. (2005) performed a factor analysis on the Buss-Durkee Hostility Inventory (BDHI) and found two factors, named as “neurotic hostility” and “aggressive hostility”. Neurotic hostility is characterized by irritability, resentment, verbal hostility and guilt, whereas aggressive hostility represents a more “cold” aggression including assault and negativism but low guilt. Individuals with the UU allele showed higher aggressive hostility but slightly lower neurotic hostility (Hennig et al. 2005), whereas LL homozygote showed higher level of impulsivity in the measurements which focused more on neurotic hostility (New et al. 1998). This may explain controversial results about the association between the polymorphisms and aggression; depending on which dimensions of aggressive behavior are measured, the association pattern may change.

In mouse models, the focus has been on the Tph2 gene, because Tph2 is preferentially expressed in the brain, whereas Tph1 is more widely distributed throughout the body (Walther et al. 2003). Mice with an R439H point mutation in the Tph2 gene have strongly reduced 5-HTP, 5-HT and its acidic metabolite levels in (Beaulieu et al. 2008). This mutant mouse showed increased aggressive behaviors in the social interaction test in a neutral arena where typically very low levels of aggression are seen (Beaulieu et al. 2008). In contrast, another polymorphism in Tph2, C1473G, which inhibits Tph2 activity in the midbrain, reduced the intensity of aggression in mice (Osipova et al. 2009). The mouse data on the R439H mutation in the Tph2 gene may be relevant to a large association study in children with attention-deficit/hyperactivity disorder (ADHD), which identified a TPH2 gene polymorphism associated with impulsivity (Oades et al. 2008).

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 levels 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 a 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 also

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. Since Pet-1 expresses specifically in the 5-HT neurons, the promoter or enhancer regions of this gene are useful for gene manipulation of 5-HT neurons (Scott et al. 2005).

Brain-derived neurotrophic factor (BDNF)—BDNF has several important roles in neuronal survival, development, differentiation and plasticity. Mice with decreased BDNF expression including knockout (BDNF^{-/-}) and conditional knockout (BDNF^{2L/1LNes-cre} and BDNF^{2L/2Lck-Cre}) all showed increased inter-male aggression (Chan et al. 2006; Lyons et al. 1999). Higher extracellular levels of 5-HT in the hippocampus was observed in BDNF^{+/-} mice compared to wild-type (Deltheil et al. 2008). However, fluoxetine could reduce heightened aggressive behavior in BDNF^{+/-} mice (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 BDNF^{2L/1LNes-Cre} and BDNF^{2L/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 considerable 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 increased aggressive behavior and changed the response to SSRI treatment (Chen et al. 2006). Conditional BDNF knockout mice using kainate receptor promoter lack BDNF expression especially in hippocampal CA3 area. These mice also showed heightened aggression compared to wild-type, suggesting an important role of hippocampal BDNF in aggression (Ito et al. 2011). 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). A further role of BDNF is evident in neuroadaptions in the VTA-accumbens pathway of mice and rats that are repeatedly attacked and show evidence for defeat, submission and disrupted social interactions (Berton et al. 2006; Miczek et al. 2011).

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 dysfunctions were 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.

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 similar aggressive behavior as wild-type mice. In contrast, when the mutant was tested as an intruder, they exhibited highly defensive reactions toward the resident. Reduced 5-HT release was observed in the dorsal raphe of α -CaMKII mutant in vitro, and thus the changed 5-HT function may be associated with defensive aggression in this mouse.

8. Concluding remarks

- Activation of 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2a/2c} receptors in mesocorticolimbic areas reduces 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. 5-HT exerts a complex role in aggression that depends on (1) the subtypes of receptors and the brain in which they are expressed, (2) the types of aggressive behaviors, and (3) the trait characteristics of the human subject or the mouse (*i.e.*, *Mus musculus* is a pugnacious species and many inbred strains are quite placid).
- Based on genetic studies, it is likely that the 5-HT_{1B} receptor has an important role in the inhibition of aggression. For other receptor subtypes such as 5-HT_{1A} or 5-HT_{2a} receptors, the association between aggressive behavior and polymorphisms in receptor genes all failed to have a reliable relationship compared to relatively consistent pharmacological data. It may be important to determine where in the brain of aggressive individuals the gene expression is changed by the polymorphisms.
- An important role of MAOA in aggressive behaviors is supported by genetic studies of deleterious mutation of MAOA gene in humans and knockout mice. In contrast to the serotonin deficiency hypothesis, these results suggest that chronically increased 5-HT levels due to reduced MAOA function - trait-like change - may promote or intensify escalated aggressive displays.
- Consistent anti-aggressive effects of S SRI treatment in several species strongly point to the serotonin transporter as a promising therapeutic target for management of impulsive, escalated aggression. More studies are required to determine the precise neurobiological mechanisms recruited for the anti-aggressive effects of SSRIs to emerge, especially as a result of chronic treatment that induces pre- and post-synaptic neuroadaptive processes.
- The genetic studies in human and nonhuman primates also suggest 5-HTT polymorphisms such as the short allele as a risk factor for violent traits, which seems to be particularly relevant in combination with environmental stress. Results from transgenic mice lacking 5-HTT are more difficult to interpret due to the wide variety of behavioral functions that are affected by the genetic manipulation.

- Gene polymorphism studies of MAOA, 5-HTT and Tph2 revealed critical gene-environment interactions as a risk factor for violent traits. Individuals with a certain allele are particularly prone to engage in violent behavior when they have a history of early life maltreatment, but the effect disappeared when they are reared in an environment with low stress.
- Modulatory mechanisms of serotonergic neurons that induce escalated aggression have gradually been identified. So far, evidence points to the modulations of activity of dorsal raphe nucleus by GABA, glutamate, CRF, and its auto-receptors as being particularly relevant to the display of escalated 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, α CaMKII, NOS, BDNF).

In the current phase of advanced molecular genetic studies, it is necessary to remind ourselves to match them with more sophisticated behavioral methodologies of aggression. It is evident that the neurogenetic mechanisms differentiate types and patterns of aggressive behavior requiring higher resolution. The current focus on brain serotonin takes advantage of the most intensively studied neural system that has been implicated in the neurogenetics of aggression. It remains astounding how such trace amounts of this indole amine can engender such profound changes in aggressive traits and states.

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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 $\pm$ 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 $\pm$ 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-HT_{1B} 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, $\pm$ 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.

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).*

A) 5-HT in mPFC

Figure 5. 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-minute samples were collected: 5 samples for baseline, 3 samples after saline injection, and 6 samples after baclofen (0.06 nmol) injection. Data are means $\pm$ SEM expressed as percentage of baseline ($n=7$); * = $p < 0.05$ compared to baseline. (B) Histological representation of probe placement in the mPFC for the microdialysis (vertical bars: 2mm probe membrane) and drug injection site in the DRN (circles). (C) The effect of 0.06 nmol baclofen (black bars) or saline (gray bars) on attack bites at different post-injection intervals (10, 40 and 100 min, corresponding to fractions 9, 11, and 14 in the microdialysis, respectively). Escalated attack bites were observed both 10 and 40 minutes after the intra-DRN baclofen injection. Values are means $\pm$ SEM; * = $p < 0.05$ compared to corresponding vehicle control. From Takahashi et al. 2010b

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 displacement, threat, pursuit, and fight.	Bennett et al. 2002 Bernstein et al. 1974 Fairbanks et al. 1999 Higley et al. 1996 Mehlman et al. 1994 Steiniger 1950 Vandenbergh 1967
Territorial resident (<i>resident intruder</i> test), mainly in mice and hamsters	Requires an established territory. In the laboratory, home-cage of experimental male (<i>resident</i>) where it is pair-housed with a female. A male stimulus animal (<i>intruder</i>) that is group housed with other males is introduced into resident's cage.	Frequency of attack bite, sideways threat, tail-rattle, pursuit, upright posture. Latency to the first bite.	Crawley et al. 1975 Eibl-Eibesfeldt 1950 Miczek and O'Donnell 1978 Van Oortmerssen and Bakker 1981
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, pursuit, upright posture. Latency to the first bite	Haney et al. 1989 Hurst 1987 Lonstein and Gammie 2002 Noiro et al. 1975 Sgoifo et al. 1992
Female aggression mainly in primates and rodents.	Dominance hierarchy among female monkeys. In the laboratory settings, female rodent pair-housed with a breeding male. Sexually mature female is introduced as an intruder.	Harrassing attacks by dominant female. Frequency of attack bite, sideways threat, tail-rattle, pursuit, upright posture. Latency to the first bite	DeBold and Miczek 1981 Palanza et al. 2005 Smuts 1986 Zitzman et al. 2005
Isolation-induced aggression (similar to territorial aggression)	Male isolated for 24 h to 8 weeks prior to <i>resident-intruder</i> encounter.	Frequency of attack bite, sideways threat, tail-rattle, pursuit, upright posture. Latency to the first bite.	Cairns and Nakelski 1971 Malick 1979 Valzelli and Bernasconi 1979 Yen et al. 1959
B. Escalated aggressive behavior.			
	Situational or Experimental variable	Agonistic behavioral measurements	References
Alcohol heightened aggression , mainly in rats and mice	Ethanol (1.0 g/kg) is injected intraperitoneally or orally or self-administered before the resident-intruder encounter.	Frequency of attack bite, sideways threat, tail-rattle, pursuit, upright posture. Latency to the first bite Targets of attack bites (head, dorsal areas, ventral areas, appendages)	Blanchard et al. 1987 Miczek and de Almeida 2001 Miczek et al 1992, 1998a Peeke and Figler 1981
Social provocation (instigation), mainly in hamsters, mice, and rats	A resident male is exposed to another male behind a protective screen in his home-cage prior to the resident-intruder encounter.		Fish et al. 1999 Heiligenberg 1974 Potegal 1991 Potegal and Tenbrink 1984
Frustration-heightened aggression	A resident male is positively reinforced. The reinforcement is abruptly omitted before the resident-intruder encounter.		Berkowitz 1993 De Almeida and Miczek 2002
Aggression induced by low glucocorticoids	Resident rats are adrenalectomized and implanted with a low-dose corticosterone pellet		Haller et al. 2001

B. Escalated aggressive behavior.			
	Situational or Experimental variable	Agonistic behavioral measurements	References
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	Hess 1954 Leyhausen 1979 Siegel et al. 1999

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 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	Chermack and Giancola 1997 Taylor 1967
The subjects are provoked by having points subtracted in a competitive task. The point losses are attributed to a fictitious opponent, but are actually random. Subjects responded by retaliation of point subtractions (= aggressive responses)	Number of point subtractions from a fictitious competitor	State	Cherek and Heistad 1971 Cherek and Lane 1999 Gowin et al. 2010
Aggression was defined as delivery of electric shocks to a fictitious opponent	Uses a modified version of the Buss aggression machine. Setting of shock level on a scale from 1–5	State	Giancola et al. 2009 Zeichner and Pihl 1979

B. Psychometric inventories			
Psychometric Assessment	Instrument	Trait/State	References
Aggression, impulsivity and hostility are measured by Minnesota Multiphasic Personality Inventory (MMPI)	Inventory	Trait	McKinley et al. 1948 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	Kim et al. 2009b Spielberg et al. 1973
Aggression is measured by Beck Anxiety Inventory and Beck Depression Inventory	Inventory	Trait	Beck et al. 1961 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	Isolation-induced aggression	Suppressed		Wersinger et al.2002
				Neutral cage aggression	Suppressed		
Adenosine 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	GAD65	2	Mix C57BL/6 and CBA2	Isolation-induced resident aggression	Suppressed		Stork et al. 2000
Calcium channel, voltage-dependent, N type, α 1B 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
β 2-microglobulin	β 2m	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
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, α 2c	Na α 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

Gene	Abb	Chr	Background strain (Generations of backcross)	Type of aggression	Effects	Serotonin function	References
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 _{40b}	6	129/SvEv	Maternal aggression	Suppressed		Del Punta et al. 2002
Oxytocin receptor	Oxtr	6	Mix C57BL/6 and 129Sv	Isolation-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 protein-binding, 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, member 2	TRP2	7	Mix C57BL/6J and 129Sv	Resident aggression	Suppressed		Stowers et al. 2002
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	ER α	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 ($\alpha 1$)	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 extracellular 5-HT	Holmes et al. 2002
Estrogen Receptor- β	ER β	12	Mix C57BL/6J and 129	Resident aggression	Increased ^{/1/}		Ogawa et al. 1999
Dopamine transporter	DAT	13	Mix C57BL/6J and 129SvJ	Dyadic encounter aggression	Increased		Rodriguez et al. 2004
5-hydroxytryptamine (serotonin) receptor 1A	5-HT _{1A}	13	129S1/Sv	Resident aggression	Suppressed	Deleted 5-HT _{1A} receptor expression	Zhuang et al. 1999

Gene	Abb	Chr	Background strain (Generations of backcross)	Type of aggression	Effects	Serotonin function	References
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 [+/-]	αCaMKII	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 α2	Cngr2	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 alcohol-related 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. 2011
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-HT _{2A/2C} : α-methyl-5-HT maleate, 0.2–1.0 µg (agonist) 5-HT _{2A/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
	Resident aggression, male mice (castrated males with hormonal replacement)	Lateral septal nucleus 5-HT _{1A} : 8-OH-DPAT*, 0.33 ng 5-HT _{1B} : CGS12066*, 18.0 ng (agonists)	8-OH-DPAT: no behavioral effects CGS: ↓ aggression with CGS, only in androgen-replacement condition; no side effects	Cologer-Clifford et al. 1997

Brain Region	Type of Aggression Species	Target; Drugs and Doses	Pharmacological Effects	References
	Alcohol-escalated aggression, male mice	<i>Lateral septal nucleus</i> 5-HT _{1B} : CP-94253, 1.0 µg (agonist)	No effects on alcohol-related or baseline aggression	Faccidomo et al. 2008
Hypothalamus	Resident aggression, male mice (castrated males with hormonal replacement)	<i>Medial pre-optic area</i> 5-HT _{1A} : 8-OH-DPAT*, 0.16 ng 5-HT _{1B} : CGS12066*, 9.0 ng (agonists)	8-OH-DPAT: ↓ aggression in androgen- and estrogen-replacement conditions; no motor effects □ CGS: ↓ aggression in androgen- and estrogen-replacement conditions; no motor effects	Cologer-Clifford et al. 1997
	Vasopressin-escalated aggression, male hamsters	<i>Anterior hypothalamus</i> 5-HT _{1A} : 8-OH-DPAT*, 0.03–3.28 ng 5-HT _{1B} : CGS12066*, 4.5–45.0 ng (agonists)	8-OH-DPAT: ↓ escalated aggression (0.33, 3.28 ng); no apparent motor effects 5-HT _{1B} : no effects on aggression (trends toward inhibition)	Ferris et al. 1999
	PAG-stimulated defensive aggression, cats	<i>Medial hypothalamus</i> 5-HT _{1A} : 8-OH-DPAT*, 0.03–1.0 µg 5-HT _{2C} : DOI*, 0.036–0.36 µg (agonists)	8-OH-DPAT: ↓ defensive hissing (0.33–1.0 µg); effect prevented by antagonist p-MPPI DOI: facilitates defensive hissing (0.36 µg); effect prevented by antagonist LY-53,857	Hassanain et al. 2003
Amygdala	Maternal aggression, rats	<i>Corticomedial amygdaloid nucleus</i> 5-HT _{1A} : 8-OH-DPAT, 0.2–2.0 µg (agonist)	↓ maternal aggression (0.5–2.0 µg); no side effects	De Almeida and Lucion, 1997
Prefrontal cortex	Resident aggression, male mice	5-HT _{1B} : CP-94253, 1.0 µg (agonist)	No effects on aggressive or non-aggressive behaviors	de Almeida et al. 2006
	Alcohol-escalated aggression, male mice	5-HT _{1B} : CP-94253, 0.5–1.0 µg (agonist)	↑ alcohol-related aggression (1.0 µg); mild increases in activity; no effects on baseline aggression	Faccidomo et al. 2008
	Alcohol-escalated aggression, male mice	5-HT _{1B} : CP-93129, 0.1–1.0 µg (agonist)	↓ baseline and alcohol-related aggression (0.1–1.0 µg); no motor effects	Faccidomo et al. submitted
Orbitofrontal cortex	Resident aggression, male mice	5-HT _{1B} : CP-94253, 0.1–1.0 µg (agonist)	↓ aggression (0.56–1.0 µg); no side effects. CP-94253 effects prevented by 1B antagonist, GR-127935.	De Almeida et al. 2006
	Maternal aggression, rats	5-HT _{1B} : CP-93129, 1.0 µg 5-HT _{1B} : CP-94253, 0.56–1.0 µg (agonists)	CP-93129: ↓ maternal aggression (1.0 µg); no side effects CP-94253: no behavioral effect	Veiga et al. 2007
	Alcohol-escalated aggression, male mice	5-HT _{1B} : CP-94253, 0.5–1.0 µg (agonist)	No effects on alcohol-related or baseline levels of aggression	Faccidomo et al. 2008
	Social instigation-escalated aggression, male mice	5-HT _{1A} : 8-OH-DPAT, 0.1–1.0 µg 5-HT _{1B} : CP-93129, 0.1–1.0 µg (agonists)	8-OH-DPAT: ↓ instigated aggression (0.56–1.0 µg); no side effects CP-93129: ↓ instigated aggression (only 0.1 µg); no side effects	Centenaro et al. 2008

DRN = dorsal raphe nucleus; MRN = median raphe 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.