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Neurogenetics of Aggressive Behavior – Studies in Rodents

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Abstract

Aggressive behavior is observed in many animal species, such as insects, fish, lizards, frogs, and most mammals including humans. This wide range of conservation underscores the importance of aggressive behavior in the animals' survival and fitness, and the likely heritability of this behavior. Although typical patterns of aggressive behavior differ between species, there are several concordances in the neurobiology of aggression among rodents, primates, and humans. Studies with rodent models may eventually help us to understand the neurogenetic architecture of aggression in humans. However, it is important to recognize the difference between the ecological and ethological significance of aggressive behavior (species-typical aggression) and maladaptive violence (escalated aggression) when applying the findings of aggression research using animal models to human or veterinary medicine. Well-studied rodent models for aggressive behavior in the laboratory setting include the mouse (*Mus musculus*), rat (*Rattus norvegicus*), hamster (*Mesocricetus auratus*), and prairie vole (*Microtus ochrogaster*). The neural circuits of rodent aggression have been gradually elucidated by several techniques e.g. immunohistochemistry of immediate-early gene (c-Fos) expression, intracranial drug microinjection, *in vivo* microdialysis, and optogenetics techniques. Also, evidence accumulated from the analysis of gene-knockout mice shows the involvement of several genes in aggression. Here we review the brain circuits that have been implicated in aggression, such as the hypothalamus, prefrontal cortex (PFC), dorsal raphe nucleus (DRN), nucleus accumbens (NAc), and olfactory system. We then discuss the roles of glutamate and γ-aminobutyric acid (GABA), major inhibitory and excitatory amino acids in the brain, as well as their receptors, in controlling aggressive behavior, focusing mainly on recent findings. At the end of this chapter, we discuss how genes can be identified that underlie individual differences in aggression, using the so-called forward genetics approach.

1. Introduction

Epigenetic studies have begun to reveal how salient life experiences during critical periods of development determine the probability of subsequently engaging in aggressive confrontations (Caspi et al. 2002; Veenema 2009). Control over the breeding history and each facet of early development make rodents the most intensively studied subjects for

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behavioral and molecular genetic analysis of aggressive behavior (Crawley et al. 1997). Since 2002, when the mapping of the mouse genome was completed (Waterston et al. 2002), mice have been the focus of most rodent aggression studies.

During the past five decades, neurogenetic research of aggressive behavior in rodents has progressed from “bottom-up” to “top-down” to epigenetic studies. Early strain comparisons and domestication studies initiated “bottom-up” genetics where the genetic basis for an aggressive trait was investigated chiefly via selective breeding (Cairns et al. 1983; Lagerspetz 1964; Popova et al. 1991; van Oortmerssen and Bakker 1981); “top-down” genetics focuses on a gene for a specific candidate receptor or transporter molecule and manipulates the expression of this gene (Cases et al. 1995; Nelson et al. 1995; Saudou et al. 1994). Given the polygenic nature of genetic influences on aggressive behavior, it is likely that future studies in rodents will uncover gene networks for each type of aggressive behavior.

The most intensively investigated neurochemical system for the control of adaptive and pathological forms of aggressive behavior involves all aspects of serotonin – which was early on labeled the “civilizing neurohumor” (Nelson and Chiavegatto 2001; Takahashi et al. 2011). Every facet of the synthetic and metabolic pathways, uptake and storage processes as well as somatodendritic, pre- and post-synaptic receptor mechanisms of serotonin has been explored in terms of its relevance to the neural control of aggressive behavior (de Boer & Koolhaas 2005; Barr and Driscoll, this volume; Bedrosian and Nelson, this volume). Several major themes have emerged from this considerable data base. For example, depletion studies have highlighted the importance of tonic levels of serotonin in the likelihood of impulsive outbursts. By contrast, inhibition of 5-HT impulse flow due to somatodendritic autoreceptor stimulation in the dorsal raphe nucleus reduces several types of species-specific and maladaptive aggressive behavior. However, activation of 5-HT1A receptors in prefrontal cortical regions can increase aggressive behavior, pointing to functionally separate receptor pools. Differences in the alleles of genes that encode for specific serotonin receptor subtypes, transporter molecules, synthetic and metabolic enzymes may contribute to variable outcomes in pharmacotherapeutic treatments. Findings of this nature have led to a re-examination of the seductively simple serotonin deficiency hypothesis of aggressive behavior. Phasic changes in 5-HT emerge during aggressive episodes as illustrated by a sudden decrease in accumbal serotonin at the termination of a confrontation (van Erp and Miczek 2000) and this decrease can be conditioned by repeated aggressive experiences (Ferrari et al. 2003).

The brain areas involved in aggressive behavior have been elucidated using traditional lesion and electrical stimulation studies. Analysis of c-Fos expression has provided novel insights into the neuronal circuits that are involved in specific types of aggressive behaviors. Intracranial microinjections of receptor-selective agonists and antagonists have demonstrated the roles of specific receptor populations in particular areas of the brain that mediate aggressive behaviors. Furthermore, recently developed optogenetic techniques have allowed *in vivo* manipulation of the activity of specific neurons in the desired brain area in milliseconds to study the role of microcircuits in aggressive behavior.

In this chapter, we will first discuss the brain circuits that have been implicated in aggression, such as the hypothalamus, prefrontal cortex (PFC), dorsal raphe nucleus (DRN), nucleus accumbens (NAc), and olfactory system. We will then discuss the roles of glutamate and γ-aminobutyric acid (GABA), major inhibitory and excitatory amino acids in the brain, as well as their receptors, in controlling aggressive behavior, focusing mainly on recent findings. The relationships between other neurotransmitters, neuropeptides, and neuromodulators that have been implicated in aggression, such as serotonin (5-HT), dopamine, vasopressin, oxytocin, testosterone, estrogen, corticotrophin releasing factor (CRF), opioids, neuronal nitric oxide synthase (nNOS) and monoamine oxidase A (MAOA), will be discussed elsewhere in this book. At the end of this chapter, we will attempt to identify genes that underlie individual differences in aggression, using the so-called forward genetics approach.

2. Rodent models for aggressive behavior

2.1 Definition of aggressive behavior

Aggression encompasses a range of diverse behavioral patterns and is multidimensional in terms of its origins, motivations, expressions and functions (Miczek et al., 2007). Definitions of aggression refer to different subtypes of aggression, or define it broadly as “behavior that inflicts harm and injury or threatens to do so” (Berkowitz, 1993) or “any form of behavior directed toward the goal of harming or injuring another living being who is motivated to avoid such treatment” (Baron and Richardson, 1994). As Scott (1966) originally defined from an ethological perspective, aggressive or agonistic behaviors are “*adaptations* for situations involving physical conflict or contests between members of the same species” (Scott, 1966). Thus, research on aggression using animal models has tended to investigate the ethological significance of the behavior, such as its functionality in the survival and reproduction of animal, and its phylogenetic and ontogenetic development. Such aggressive behavior is beneficial to the individual because this behavior can be used to obtain food, water and other resources, including female mates in the case of males, and to defend its territory, offspring, or social rank. However, given that aggressive behavior carries the associated risks (costs) of injury or even death as well as high energy expenditure, the exercise of aggressive behavior is determined by a *cost-benefit* analysis (Maynard Smith and Price, 1973; Haller, 1995). When this balance is disrupted and an animal shows an exaggerated level of aggression, the behavior is no longer adaptive, and it could be called maladaptive or pathological aggression. Most research on aggression in both human and veterinary medicine seeks to understand and control pathological aggression (Volavka and Nolan, 2008; Siever, 2008).

Aggressive behavior in rodent models can be classified as “*offensive*” or “*defensive*” based upon the distal and proximal antecedent conditions that precipitated it, the topography of the behavior, and its consequences (Blanchard and Blanchard, 1977; Brain, 1979; Adams, 2006). Offensive aggression is observed in interactions between mature males, and most of the research on the genetics and neurobiology of aggression studies this offensive behavior (Table 1A). In rodents, offensive aggressive behavior between conspecifics is ritually organized, composed of sideways threats, chasing, tail rattling (especially in mouse),

defensive upright postures, and attack bites (Miczek and O'Donnell, 1978). The attack is usually directed toward less vulnerable body areas such as the back and flanks of the opponent (Blanchard and Blanchard, 1977; Blanchard et al., 1979, 2001). Defensive aggression involves attack in defense of the self; it occurs in response to threatening or fear-inducing stimuli, and is often accompanied by escape. In male rodents, specific defensive behaviors include escape, freezing, defensive postures, and threats, with defensive attacks targeted at the snouts of predators or conspecifics (Blanchard and Blanchard, 2003).

In most common laboratory rodents, aggressive behavior is restricted almost exclusively to males. However, both male and female golden hamsters show a high level of aggression, with females usually dominating males (Payne and Swanson, 1970). Females of many rodent species show intense aggressive behavior during specific periods after giving birth, referred to as maternal aggression, this protects their newborn offspring from male intruders (Palanza et al., 1994). In most rodents, female aggressive behavior becomes more frequent shortly before gestation, reaches a peak at the first week postpartum, and declines thereafter (Noirot et al., 1975; Erskine et al., 1980). Maternal aggression includes both defensive and offensive elements; lactating females engage in defensive attacks toward males and offensive attacks toward female intruders (Parmigiani et al., 1989; Lucion and de Almeida, 1996; de Almeida et al. this volume). In some respects, infanticide (Svare et al., 1984), predatory aggression, such as mouse killing behavior by rats (Karli et al., 1972), and play fighting in juvenile rats and hamsters (Pellis and Pellis, 1988; Pellis and Iwaniuk, 2000) also qualify as aggressive behavior. However, these are considered to be qualitatively different from offensive or defensive aggression. Each type of aggression is most likely regulated by different genes and neurobiological pathways, with some overlap.

2.2 Escalated aggression

Aggressive behavior in animals becomes increasingly relevant to clinical concerns in humans when it differs from the typical pattern for the species in question. Aggressive behaviors that exceed species-typical levels or patterns are known as *escalated aggression*, or sometimes as maladaptive or pathological aggression that models violent behavior in humans. Several rodent models have been used to investigate the neurobiology and genetics of escalated aggression (Miczek et al., 2013; Table 1B). Escalated aggression is characterized quantitatively by shorter attack latencies (readiness to initiate aggressive behavior) and higher frequencies and longer durations of fighting (inability to terminate aggressive behavior) than normal adaptive aggression (Miczek et al., 2004; de Almeida et al., 2005). There are also qualitative differences. Attack bites aimed with high intensity at vulnerable parts of the opponent's body, such as the head and throat, are considered to be abnormally aggressive, while adaptive aggression consists of less-injurious bites directed at the intruder's back and flanks (Haller and Kruk,2006). Additional qualitative distinctions between adaptive and escalated aggression include context-independent attacks regardless of the sex and nature of the opponent, such as the responsiveness of the target (moving and responsive vs. anaesthetized), or the test environment (home or neutral cage), a failure to respond to appeasement signals, and a lack of ritualistic behaviors, quantified using Attack/Threat (A/T) ratios (Haller et al., 2005a, 2006; de Boer et al., 2009). Therefore, in principle, "violence" in animal models could refer either to quantitatively escalated and to

qualitatively abnormal forms of aggression (for review see Natarajan and Caramaschi, 2010; Miczek et al., 2013).

3. The neurobiology of aggressive behavior in rodents

3.1 Brain circuits activated by aggressive encounters

To understand the neural circuits involved in aggressive behaviors, immediate early gene expression has been analyzed to identify brain areas that are activated by aggressive acts. c-Fos is the protein product of an immediate early gene, *fos*, which is expressed in neurons shortly after their depolarization (activation), and then induces the expression of downstream genes. The expression of c-Fos can be readily visualized by immunohistochemistry staining, and the number of c-Fos positive neurons in each brain area is used to quantify the activation of the area. Investigations of c-Fos activity have implicated several brain areas in aggressive behavior: the PFC; the medial preoptic area (MPOA); lateral septum (LS); some hypothalamic nuclei including the anterior hypothalamus (AH), ventromedial hypothalamus (VMH) and lateral hypothalamus (LH); the paraventricular nucleus (PVN); the medial and central amygdala (MeA and CeA); bed nucleus of the stria terminalis (BNST); the periaqueductal gray (PAG); the locus coeruleus (LC); and the DRN (for review, see Lonstein and Gammie, 2002; Nelson and Trainor, 2007; Heinz et al., 2011).

Many of these areas are involved in aggressive behavior in non-human primates, and even in humans (Nelson and Trainor, 2007). Note, however, that these areas are not specific to aggressive behavior but are also involved in a wide range of other social behaviors (Newman, 1999). Figure 1 summarizes the brain areas that are activated by intermale aggressive behavior, maternal aggressive behavior, and escalated aggressive behavior, as indicated by c-Fos expression. There is a large overlap among brain areas that are involved in different types of aggression, but also some differentiation. In particular, when the animal is engaging in escalated levels of aggression, activity in some brain areas may be either overactivated or suppressed, depending on the model of escalated aggression, when compared with the species-typical level (Figure 1). For example, the PAG is involved in both intermale and escalated aggression (and phosphorylation of the cAMP response element binding protein (pCREB) suggests the involvement of the PAG in maternal aggression). The PAG is activated during species-typical aggression, but at the same time, the degree of PAG activation is inhibited in animals that show escalated aggression as a result of selective breeding compared to a line that is selected for low aggression (Kollack-Walker and Newman, 1995; Delville et al., 2000; Gammie and Nelson, 2001; Haller et al., 2006).

3.2 Hypothalamus and aggression

Lesion or stimulation studies have confirmed the involvement of each brain area of the aggression circuit in aggressive behavior. Of all of the areas of the brain, the hypothalamic area is one of the best-studied areas in relation to aggression, ever since this area in aggression in cats was identified in the early 20th century (Hess and Akert, 1955). The hypothalamic attack area (HAA) is a region containing several hypothalamic nuclei where electrical stimulation can elicit attack behavior (Kruk et al., 1983; Siegel et al., 1999).

Electrical stimulation of parts of the HAA, such as lateral or ventromedial hypothalamus, also induces escalated aggression in the rat, with the resulting behavioral pattern not simply categorized as “offensive” or “defensive” aggression but rather as a mixed combination of several types of aggression (Siegel et al., 1999). This hypothalamically induced attack behavior can be directed against males, females, anesthetized or dead rats, and even mice (Koolhaas, 1978; Kruk, 1991; Roberts and Nagel, 1996). Also, observation that the attack is directed toward vulnerable areas of the body of the opponent suggests that the aggressive behavior induced by stimulation of the hypothalamic area represents abnormal or pathological aggression. One of the neuromodulators in the hypothalamus with a strong link to the level of aggression is arginine vasopression (AVP) (Donaldson and Young, 2008). In male hamsters, microinjection of AVP into the anterior or ventrolateral hypothalamus enhances aggressive behavior, whereas antagonists for the AVP receptor V1aR reduces aggressive behavior (Ferris and Potegal, 1988; Potegal and Ferris, 1989; Ferris et al., 1997; Caldwell and Albers, 2004). The effect of intra-hypothalamic AVP on aggression depends on the photoperiod, the basal testosterone level, and the sex of the individual (Delville et al., 1996; Caldwell and Albers, 2004; Gutzler et al., 2010). The HAA is further discussed in detail by (Kruk, this volume).

Recently developed optogenetic techniques (Deisseroth et al., 2006) have shown that manipulation of phasic activity of the hypothalamic attack area can elicit aggressive behavior in mice (Lin et al., 2011). In this method, genetic manipulation to artificially express light-sensitive opsin receptors (i.e. channelrhodopsin ChR2) that are derived from other organisms (such as *Chlamydomonas*) on desired mouse neurons enables light stimuli to activate or inhibit target neurons in milliseconds. Phasic activation of the ventrolateral area of the ventromedial hypothalamus (VMHvl) of male mice, using optical stimulation of artificially expressed ChR2, provoked attacks towards either male or female opponents, and even against inanimate objects (Lin et al., 2011). Attacks started and stopped concurrently with the onset and termination of the light stimulus, suggesting that VMHvl is a switch that controls the execution of attack behavior. However, Lin et al. (2011) used a promoter that is active in all neurons within the VMHvl region, so all types of neurons within the VMHvl area expressed ChR2. The key advantage of optogenetics over electrical stimulation is that it can be used to manipulate a specific type of neuron or a specific neural circuit. By using specific promoters, such as the CaMKIIα promoter which is specifically expressed in excitatory neurons, or parvalbumin (PV) promoter which is specifically expressed in GABA neurons, it is possible to express ChR2 or other opsins in a specific type of neuron and to manipulate the activity of these subpopulations of neurons specifically. Thus, optogenetic techniques can be used to dissect the functional microneurocircuit in the hypothalamic area that is associated with aggressive behavior. For example, optogenetics techniques can be applied to determine whether AVP projections from the medial supraoptic nucleus (mSON) or the nucleus circularis (NC) into the anterior hypothalamus facilitate aggressive behavior (Ferris et al., 1997).

3.3 Prefrontal cortex (PFC) and aggression

The importance of the PFC in the inhibitory control of aggression has been reported in primates, including humans (Nelson and Trainor, 2007). The PFC sends glutamatergic

projections to several brain areas that are linked to aggression, such as the hypothalamus, amygdala, and DRN (Peyron et al., 1998; Rosenkranz and Grace, 2002; Hoover and Vertes, 2011). In rodents, the PFC also has some regulatory roles in aggressive behavior. Among several subareas in the PFC, the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC) are activated in rats and mice engaged in inter-male aggression (Haller et al., 2006; Halász et al., 2006; Wall et al., 2012), or by winning the social dominance test in mice (Wang et al., 2011). The activation of the mPFC was blunted in socially isolated rats after 4 weeks of isolation (Wall et al., 2012). In addition, bilateral lesions of the OFC increased inter-male aggression in the rat (De Bruin et al., 1983). Recently, we used the optogenetic technique with the aim to modulate the activity of mPFC excitatory neurons during an aggressive encounter in the male mouse. Our data show that the activation of the mPFC, but not ventral OFC, inhibits inter-male aggressive behavior specifically, without affecting any other behaviors (Takahashi et al., unpublished data). We conclude that themPFC has an important inhibitory role on aggression so that it is maintained at species-typical level of aggression.

Serotonin (5-HT) receptors seem to have an important role in modulating the activity of the PFC and therefore in inhibiting aggressive behavior. For example, microinjection of the 5-HT_{1B} agonist CP-94,253 into the ventral OFC suppressed inter-male aggression, maternal aggression, and aggression induced by social instigation (De Almeida et al., 2006; Veiga et al., 2007; Centenaro et al., 2008). The activation of 5-HT_{1B} receptors in the mPFC also reduced species-typical territorial aggression (Faccidomo et al., 2012). On the other hand, the same treatment escalated aggressive behavior when it was microinjected into the mPFC, but not into the OFC, under the effect of alcohol (Faccidomo et al., 2008). *In vivo* microdialysis showed that the extracellular level of 5-HT in the mPFC is reduced during and after a species-typical aggressive encounter in rats (Van Erp and Miczek, 2000; Figure 2). By contrast, pharmacological treatment that induced escalated aggression caused a phasic increase of 5-HT in the mPFC (Takahashi et al., 2010c; Figure 3). Furthermore, the dominant male mouse in a group-housed cage showed higher mPFC activity in terms of glutamatergic synaptic transmission and c-Fos expression, and the genetic manipulation of the gulutamatergic AMPA current in the mPFC caused a change of social rank in the cage (Wang et al., 2011). Therefore, the PFC modulates several types of aggressive behaviors in different ways.

3.4 Dorsal raphé nucleus (DRN) and aggression

Since its discovery in the brain, 5-HT has been considered a key transmitter in the neurocircuitry that controls aggression in several species ranging from invertebrates to humans (Coccaro et al., 1997; Miczek et al., 2004; 2002; Olivier, 2004; de Boer and Koolhaas, 2005; Takahashi et al., 2011). 5-HT in the mammalian central nervous system originates mainly from the midbrain raphé nuclei. In particular, the DRN contains the largest accumulation of 5-HT neuronal cell bodies in the brain, and it sends afferent projections to several distinct targets including the limbic structures and cortex (Dahlström and Fuxe, 1964; Azmitia and Segal, 1978; Michelsen et al., 2007). Firing rates of DRN neurons increase in distinct patterns during defensive and offensive fighting in treeshrews (Walletschek and Raab, 1982). In rats, c-Fos expression is increased in the 5-HT neurons of

the DRN after an aggressive encounter (Van der Vegt et al., 2003). The activity of the DRN is modulated by its own released 5-HT via autoreceptors, and also by GABA, glutamate, norepinephrine and neuropeptides such as CRF (Adell et al., 2002). Activation of 5-HT_{1A} and 5-HT_{1B} autoreceptors in the DRN by microinjection of selective receptor agonists consistently reduced aggressive behavior in rats and mice, but in the case of 5_HT_{1A} receptor agonists with concomitant reduction of motor activity and social interactions (Mos et al., 1993; Bannai et al., 2007; Faccidomo et al., 2008). GABA receptors in the DRN seem to have a more aggression-specific effect. Administering baclofen, a $GABA_B$ receptor agonist, into the DRN escalated intermale aggressive behavior in the mouse (Takahashi et al., 2010c). Interestingly, administration of the $GABA_A$ receptor agonist muscimol into the DRN only heightened aggressive behavior in mice after consuming a modest amount of alcohol (Takahashi et al., 2010a). By contrast, intra-DRN administration of muscimol either reduced aggressive behaviors in rats (Van der Vegt et al., 2003) or had no effect on aggression (Takahashi et al., 2010c) in the absence of alcohol. This pattern of effects suggests that both subtypes of GABA receptors are involved in escalated forms of aggressive behavior via different mechanisms. *In vivo* microdialysis showed that $GABA_B$ activation in the DRN increased the extracellular level of 5-HT in the mPFC (Takahashi et al., 2010c). This suggests that the activation of DRN 5-HT neurons occurs during escalated inter-male aggression (Figure 3).

By contrast, there is evidence for inhibition of 5-HT neurons during escalated aggression. Audero et al (2013) used transgenic mice with overexpression of 5-HT1A receptors specifically located on soma of 5-HT neurons after adulthood (>P40). These mice showed suppressed 5-HT neural firing in both dorsal and median raphe nuclei, and also showed enhanced aggressive behavior. Pharmacological inhibition of raphe 5-HT neural firing in these mice also increased attack bites, suggesting that transient inhibition of 5-HT neurons can escalate mouse aggression (Audero et al 2013). CRF in the DRN also has an important modulatory effect on aggressive behavior. Local administration of the CRF1 receptor antagonists CP-154526 or MTIP into the DRN prevented the escalation of aggression induced by alcohol consumption without producing any motor incoordination, whereas an antagonist for another receptor subtype, CRF2, enhanced inter-male aggressive behavior in male mice (Quadros et al., 2009). The anti-aggressive effect of the CRF1 antagonist required intact 5-HT neural activity in the DRN, suggesting that the activation of 5-HT neurons suppresses heightened aggression specifically when under the influence of alcohol (Quadros et al., 2009). Furthermore, there are some lines of knockout mice that show enhanced aggression with reduced 5-HT content or 5-HT neural activities (e.g. gene knockout of TPH2, Pet1, or α-CaMKII) (Chen et al., 1994; Hendricks et al., 2003; Alenina et al., 2009; Mosienko et al., 2012; Angoa-Pérez et al., 2012).

It still needs to be determined under which conditions the DRN 5-HT neurons are activated or inhibited during which type of escalated aggression. It is likely that the basal level of 5-HT (*trait*) and phasic changes of 5-HT (*state*) may have different roles in the different types of aggression. Direct recording of 5-HT neuron activity during aggressive encounter, or optogenetic activation of the DRN 5-HT neurons will clarify the role of phasic activity of 5-HT neurons in the DRN on aggressive behavior.

3.5 Nucleus Accumbens (NAc) and aggression

Aggressive behavior has a rewarding property for dominant males, and the opportunity for aggressive encounters reinforces conditioned responses in male mice (Fish et al., 2002, 2005). Microinjection of either a dopamine D1 or D2 receptor antagonist into the NAc reduced this operant response, which suggests that the rewarding property of an aggressive encounter is mediated by dopamine receptors in the NAc (Couppis and Kennedy, 2008). The mesocorticolimbic dopamine system, which comprises DA neurons in the ventral tegmental area (VTA) and their projections to the NAc and other brain areas, is known to mediate reward processing in addition to aversive motivation (Kelley et al 2002). *In vivo* microdialysis showed that the level of dopamine in the NAc increased during and after an aggressive confrontation in male rats (Van Erp and Miczek, 2000; Ferrari et al., 2003; Figure 2). After repeated aggressive encounters at the same time of day, resident rats showed an anticipatory increase in dopamine levels, and a decrease in 5-HT, in the NAc at the scheduled time, even without aggressive behavior (Ferrari et al., 2003). On the other hand, defeated male rats also showed increased dopamine release in the NAc (Tidey and Miczek, 1996; Anstrom et al., 2009). Thus, the increase of dopamine in the NAc does not simply indicate the reward signal *per se*, but characterizes both individuals reacting to an aggressive confrontation and anticipating such an event (Miczek et al., 2007).

3.6 Olfactory system and aggression

For rodents, olfaction is the major sensory input regulating social behaviors (Brennan and Keverne, 2004). Olfactory information about an intruder is first processed by the olfactory bulb, and then projected to the amygdala via the lateral olfactory tract. Thus, the olfactory system is the first location for evaluating the quality of the opponent (Guillot and Chapouthier, 1996). There are two types of olfactory bulb, the main and accessory olfactory bulbs; whereas the main olfactory bulb receives all of the odorant information, the accessory olfactory bulb specifically receives pheromonal information, which is important for intraspecific communication (Dulac and Torello, 2003). Dominant male rodents show territorial scent marking (Desjardins et al., 1973), and their urine contains aggression-promoting pheromones, so-called major urine proteins or MUPs (Chamero et al., 2007). In addition, two volatile compounds, dihydroexobrevicomin and 2-(s-butyl)-dihydrothiazole, have been identified as pheromones in male urine that can elicit inter-male aggression. However, these pheromones need to interact with other components of urine (Novotny et al., 1985). The chemoreceptors for the pheromones reside on the sensory neurons of the vomeronasal organ (VNO), and send their axons to the accessory olfactory bulb. It has been shown that lesions of the VNO produce a wide range of deficits in social and reproductive behaviors including inter-male aggression and maternal aggression (Clancy et al., 1984; Bean and Wysocki, 1989). Similarly, deletion of genes that relate to VNO signaling reduce aggressive behaviors and the capacity to discriminate between the sexes (Stowers et al., 2002; Keverne, 2002; Norlin et al., 2003; Chamero et al., 2011). TRP2 is a putative cation channel that is exclusively expressed in VNO sensory neurons, and deletion of TRP2 in the mixed background of the C57BL/6J and 129/SvEv mouse (TRP2−/−) induced an absence of urine-evoked neuronal activity in the VNO. Male TRP2−/− mice showed complete abolition of aggressive behavior, and they also engaged in sexual behavior toward male intruders

(Stowers et al., 2002; Leypold et al., 2002). In addition, lactating female TRP2−/− mice exhibited a reduced level of maternal aggression with either the C57BL/6J and 129/SvEv mixed background (Leypold et al., 2002) or the genetic background of a high maternal aggression line (Hasen and Gammie, 2009). Pheromone receptors are encoded by two distinct super families of genes, V1R and V2R, and these receptors are located on a separate layer of the VNO (Dulac and Axel, 1995; Tirindelli et al., 1998). Deletion of the V1R family cluster (including sixteen V1R genes) on the 129/SvEv background reduced maternal aggressive behavior in lactating females (Del Punta et al., 2002). However, failure to discern a difference in the initiation of aggressive behavior in male V1Rs mutant mice compared with wild-type mice suggests that the V1R-expressing VNO neurons specifically transmit the signals for female aggression. On the other hand, hypoactivity of V2R-expressing VNO neurons, induced by the conditional knockout of a G protein (Gαo) being regulated by the promoter of the olfactory marker protein (OMP), reduced both inter-male aggression and maternal aggression (Chamero et al., 2011). In that study, the intruder male was castrated and then scrubbed with recombinant MUP protein because it has been shown that the MUPs activate V2Rs (Chamero et al., 2007, 2011). Thus, V2R-expressing VNO neurons recognize urine-containing pheromones and subsequently trigger aggressive behavior in both sexes.

4. Excitatory and inhibitory neurotransmission and aggression

4.1 Glutamate and aggression

Glutamate is the major excitatory transmitter in the mammalian brain. Several kinds of psychiatric diseases such as anxiety disorders, depression, and also aggression are attributed to an imbalance between glutamatergic excitation and GABAergic inhibition in limbic areas (Herman et al., 2004; Miczek et al., 2007; Garcia-Garcia et al., 2009). In particular, activation of glutamate neurons in the hypothalamic attack area (HAA) seems to be strongly linked to aggression. Direct microinjection of L-glutamate into the HAA induced aggressive responses in cats (Brody et al., 1969). In rats, microinjecting a combination of the glutamate receptor agonist kainate and the $GABA_A$ receptor antagonist bicuculline into the HAA induced an increase in attack behavior (Haller et al., 1998). This pro-aggressive effect depended on previous experience; rats with recent aggressive experiences showed an increase in aggressive behavior, whereas naïve animals displayed grooming in response to the same treatment. Male hamsters treated with anabolic-androgenic steroid (AAS) during adolescence displayed both highly escalated levels of offensive aggression and increased activation of glutamatergic neurons in several brain areas, including the anterior hypothalamus (Fischer et al., 2007; Carrillo et al., 2009, 2011). We also found that direct microinjection of L-glutamate in the DRN escalate aggressive behavior of male mice. Furthermore, *in vivo* microdialysis showed that glutamate release in the DRN was increased in mice that engaged in aggressive behavior (Takahashi et al unpublished data).

There are three main types of ionotropic receptor for glutamate: N-methyl-D-asparate (NMDA) receptors, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) receptors, and kainate receptors. All of these receptors are cation channels and depolarize the surrounding membrane. The AMPA receptors and kainate receptors are responsible for fast excitatory transmission mediated by the influx of Na+ ions. In contrast, NMDA

receptors have a higher permeability to Ca^{2+} than AMPA receptors but require membrane depolarization in order for Ca^{2+} influx to release Mg^{2+} block from the NMDA cation channel. Accordingly, NMDA receptors open more slowly than AMPA receptors. Glutamate also activates a distinct class of G-protein coupled receptors, called metabotropic glutamate receptors (mGluRs) (Kew and Kemp, 2005). As a consequence of this diversity of receptor types for glutamate, it is likely that the roles of glutamate and its receptor subtypes in aggression differ.. Most pharmacological studies of glutamate and aggression focused primarily on the NMDA receptor because of the availability of selective pharmacological agents. However, the role of other receptors in aggression has been discovered gradually by using gene knockout mice and novel pharmacological tools.

4.1.1 NMDA receptors—Pharmacological studies have shown that antagonists of NMDA receptors tend to have biphasic effects on aggression, causing an escalation of aggression at low doses and suppression of aggression at higher doses. However, the nature and the extent of the response are affected by the individual's basal level of aggression and/or housing conditions. Systemic administration of prototypic antagonists of NMDA receptors such as phencyclidine (PCP) or dizocilpine (MK-801) can increase aggressive behavior in the mouse and rat, depending on the individual's age and specific history such as how long the individual has been housed in isolation, the extent of sleep deprivation, or the presence or absence of previous aggressive encounters (Russell et al., 1984; Wilmot et al., 1987; McAllister, 1990; Lang et al., 1995; Audet et al., 2009). In contrast, high doses of PCP and dizocilpine reduce aggressive behavior and cause abnormal locomotor activation or ataxia (Tyler and Miczek, 1982; Miczek and Haney, 1994; Lang et al., 1995; Belozertseva and Bespalov, 1999). Memantine, the low-affinity NMDA receptor channel blocker, also reduced aggressive behavior in socially isolated male mice when used at the highest dose which induced ataxia (Belozertseva and Bespalov, 1999). In mice that showed increased aggression induced by morphine withdrawal, memantine specifically reduced aggressive behavior without any side effects (Sukhotina and Bespalov, 2000). On the other hand, memantine and neramexane, another non-competitive NMDA receptor blocker, enhanced territorial aggressive behavior in male mice after alcohol consumption (Newman et al., 2012; Figure 4). In each case, control animals that were not treated with morphine or alcohol did not show any aggression-specific effect of memantine (Sukhotina and Bespalov, 2000; Newman et al., 2012). Anatomically discrete analysis is required to identify the sites of action for NMDA receptors that produce escalated aggressive behavior.

The NMDA receptor is a heterotetramer that comprises mainly two NR1 subunits and two NR2 subunits (NR2A–NR2D) (Monyer et al., 1992; Kutsuwada et al., 1992). Geneticists have generated knockout mice to examine the role of the NMDA receptor in behavior. Unfortunately, given that complete ablation of NMDA receptor expression in NR1- or NR2B- knockout mouse lines causes lethality during the prenatal period, adult behaviors cannot be studied in these mice (Li et al., 1994; Forrest et al., 1994; Kutsuwada et al., 1996). However, there is a mutant mouse with reduced NMDA receptor expression but with normal development. A mouse mutant affected in the NR1 subunit (Nr1neo−/−) expresses 5% to 10% of the normal level of the NR1 subunit of the NMDA receptor; these mice show strongly reduced social investigation and therefore rarely show aggressive behavior (Mohn

et al., 1999; Duncan et al., 2004). This mutant mouse also shows a range of abnormal behaviors, such as hyperactivity, deficits in sensorimotor gating, and reduced motivation to find hidden food (Mohn et al., 1999; Duncan et al., 2004). Those pleiotropic changes in various other phenotypes may contribute to the reduction of aggression in this mutant mouse.

The function of the NMDA receptor in the PFC has an important role in a well-known model for escalated aggression induced by the deficiency of monoamine oxidase A (MAOA; Bedrosian and Nelson, this volume). As in humans, disruption of the MAOA gene in either a C3H/He or 129S6 mouse genetic background escalated aggressive behavior in males such as infliction of skin wounds on cage mates and short attack latency in the resident-intruder test (Cases et al., 1995; Scott et al., 2008). In addition to large increase of 5-HT and norepinephrine, which are normally degraded by MAOA, in the developing brain, MAOA knockout mice showed altered expression of the NMDA receptor subunits in the PFC; higher expression of NR2A and NR2B subunits as well as reduced levels of glycosylated NR1 compared with those in wild-type mice (Bortolato et al., 2012). These alterations reduced NMDA-mediated fluctuations in the amplitude and decay time of excitatory postsynaptic current (EPSC) in the PFC, and a moderate dose of dizocilpine or antagonists for either NR2A or NR2B reduced aggressive behavior in MAOA knockout mice without affecting locomotion (Bortolato et al., 2012). Thus, changes in the composition of the NMDA receptor subunit in the PFC seem to critically contribute to the genesis of pathological aggression in MAOA-deficient mice.

Further evidence points to the involvement of NMDA receptor subtypes in aggression. Rearing in social isolation causes rats to increase their aggressive behavior, and these rats showed increased expression of NR2A and NR2B subunits in the hippocampus, but reduced NR2A expression in the PFC (Zhao et al., 2009). Chronic exposure to AAS, another treatment that facilitates aggression, decreased the abundance of the mRNA that encodes the NR2A subunit in the hippocampus and hypothalamus, but not in the cortex, of male rats (Le Grevès et al., 1997).

4.1.2 AMPA receptors—Dominant male C57BL/6 mice in group-housed home cages, assessed using the tube-test (Table 1), have higher AMPA-mediated current in mPFC pyramidal neurons than otherwise comparable subordinate males (Wang et al., 2011). Artificial overexpression of AMPA receptors in mPFC pyramidal neurons induced by viral infection increased social rank in the home cage, whereas the suppression of AMPA receptor expression in the mPFC reduced the social rank (Wang et al., 2011). Thus, AMPA receptor-mediated activation of the mPFC seems to have an important role in social hierarchy and aggressive behavior. The AMPA receptors are heterotetramers assembled from four subunits, GluR1–GluR4, with GluR1/2 and GluR2/3 combinations mainly form ion channels with distinct functional properties (Hollmann and Heinemann, 1994; Derkach et al., 2007). Knockout mice that lack the GluR1 (GluRA) subunit, as well as mutant mice that have a mutation in GluR1 which causes functional reduction of the AMPA receptor, were less aggressive than their wild-type littermates (Vekovischeva et al., 2004). Whereas males of both classes of mutants showed reduced aggressive behavior in their territory after prolonged isolation (30 days) and in a neutral environment, female GluR1 knockout mice

did not show altered maternal aggressive behavior (Vekovischeva et al., 2004). GluR1-containing AMPA receptors co-localize with androgen receptors in hypothalamic neurons, and castrated rats exhibited lower levels of GluR1 protein expression in the hypothalamus compared with intact rats or castrated rats treated with either testosterone or estrogen (Diano et al., 1997). In addition, AAS-treated Syrian hamsters showed an increased number of neurons that express GluR1-containing AMPA receptors in the ventrolateral hypothalamus and BNST (Fischer et al., 2007). These results consistently suggest that GluR1 subunit-containing AMPA receptors in several brain areas, including the mPFC, hypothalamus and BNST, promote aggressive behavior in male rodents. On the other hand, male GluR3 knockout mice with the C57BL/6J background fought more relative to wild-type males (Adamczyk et al., 2012). Overall, the GluR1-containing AMPA receptor and GluR3-containing AMPA receptor have opposite effects on the modulation of aggressive behavior.

In addition to the functional differences among the subtypes of glutamate receptor, differences in location are critical for their effect on aggression. To dissect the effect of each receptor in a specific neuron, a conditional knockout mouse has been established with deletion of the receptor gene in a specific neuron at a specific developmental stage. For example, a conditional knockout of the AMPA receptor GluR2 subunit that is expressed specifically in hypothalamic gonadotropin-releasing hormone (GnRH) neurons, has been established on the mixed genetic background of C57BL/6 and NMRI strain of mice; these mutants lack many kinds of social behavior and thus rarely produce offspring (Shimshek et al., 2006). Male GnRH GluR2 knockout mice showed a lack of interest in females and also displayed no aggressive behavior toward male intruders. Females with this mutation also showed impaired maternal care and no maternal aggression. Conditional knockout and overexpression techniques will allow more detailed dissection of the neuronal pathway that is involved in aggressive behavior.

4.2.3. Kainate receptor and delta receptors—The kainate receptor, which is an ionotropic receptor for glutamate, comprises five subunits, GluR5–GluR7 and KA1–KA2. A human genome-wide association study identified the gene that encodes a subunit of the kainate receptor, GluR6 (GRIK2), as potentially conferring susceptibility to bipolar affective disorder (Hamshere et al., 2009). Deletion of the GluR6 gene subunit in mice induced manic-like behavioral changes, and GluR6 knockout mice are hyperactive, more aggressive toward other males, and exhibited less depressive-like behavior (Shaltiel et al., 2008). These behavioral phenotypes in knockout mice were reversed by chronic treatment with lithium.

The last family of ionotropic glutamate receptors comprises the delta receptors. The function of delta receptors remains poorly understand. However, a recent study has shown that mice with deletion of GluD1 on the mixed background of C57BL/6J and 129/SvEv displayed an increased number of attacks and shorter attack latency compared with characteristically non-aggressive wild-type mice in the resident-intruder test after 3 weeks of isolation (Yadav et al., 2012). These GluD1 mutants showed increased expression of the GluR1 (AMPA receptor) and GluR6 (kainate receptor) subunits in the amygdala. As mentioned above, GluR1-containing AMPA receptors seem to promote aggressive behavior. Accordingly, increased GluR1 levels in the amygdala might account for the escalated aggressive behavior of these mutants compared with their wild-type littermates. However, these mutants showed

reduced GluR1 expression in the PFC. It is also possible that activation of the GluD1 receptor itself may have a role in regulating aggression circuits. The emergence of novel and more selective drugs for each of these receptor subtypes promises to elucidate their specific aggression-modulating effects.

4.2.4. Metabotropic glutamate receptors (mGluRs)—There are three groups of mGluRs, which are classified as group I (mGluR1, 5), group II (mGluR2, 3), and group III (mGluR4, 6, 7, 8) mGluRs. The group I receptors couple with G-protein alpha-q (Gq) to activate the phospholipase C (PLC)-inositol trisphosphate (IP3) cascade. In contrast, group II and III receptors couple with inhibitory Gi/o, which decreases the activity of adenylate cyclase (Kew and Kemp, 2005). Regarding aggressive behavior, mGluRs have been studied much less than ionotropic glutamate receptors. A few studies have examined the effects of recently developed mGluR-specific agents on aggression.

Goup I (mGluR1, 5): Pharmacological manipulation of group I mGluRs demonstrated their roles in promoting inter-male aggression. A selective antagonist of mGluR1, JNJ16259685, suppressed isolation-induced aggression in male mice without any concurrent motor effects (Navarro et al., 2008). The mGluR5 antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) also reduced aggressive behavior in both socially isolated and pair-housed male mice in a dose-dependent manner (Navarro et al., 2006; Newman et al., 2012). On the other hand, in alcohol-treated animals a low dose of MTEP escalated aggressive behavior (Newman et al., 2012). Therefore, as with NMDA receptor antagonists, the interaction of Group I mGluRs with ethanol to escalate aggressive behaviors remains to be resolved.

Group II (mGluR2,3): In contrast to group I mGluRs, group II mGluRs seem to inhibit aggression. The mGluR2/3 receptor selective agonist LY379268 reduced inter-male aggressive behavior at a high dose, but this dose also reduced locomotor activity (Newman et al., 2012). Another mGluR2/3 agonist, MGS0028, also reduced aggressive behavior in socially isolated (SI) mice. This drug also inhibited hyperactivity in SI mice, causing to return it to the level shown by group-housed males, but had no effect on the group-housed males (Ago et al., 2012).

Group III (mGluR4,6,7,8): A selective agonist for mGluR7 receptors, AMN082, reduced offensive behaviors such as attack and threat without affecting locomotor activity. However, the mGluR8 agonist (S)-3,4-DCPG did not produce significant behavioral changes in male mice (Navarro et al., 2009). It is possible that group III mGluRs have a similar inhibitory effect on aggression to that of group II mGluRs, because both groups of mGluR couple with inhibitory Gi/o. However, their site of action varies due to the different localization of these mGluRs (Shigemoto et al., 1997).

4.2 GABA and aggression

GABA is the major inhibitory neurotransmitter in the central nervous system. Early reports hypothesized that the loss of GABAergic inhibitory control of the limbic system causes exaggerated aggression (Mandel et al., 1981). Comparisons of GABA contents or the

activity of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD), in the postmortem brains of male mice and female hamsters supported this hypothesis; aggressive animals showed a lower GABA level and lower GAD activity in several brain areas such as the olfactory bulb, striatum, and amygdala, when compared with nonaggressive animals (Earley and Leonard, 1977; Simler et al., 1982; Potegal et al., 1982; Clement et al., 1987; Guillot and Chapouthier, 1998). On the other hand, gene knockout of a 65-kDa isoform of GAD (GAD65) in mice with a mixed background of C57B/6 and CBA2 induced a decrease in brain GABA content during postnatal development, and these mutant males showed reduced aggressive behavior toward male intruders after four weeks of isolation (Stork et al., 2000). Furthermore, in animal models of escalated aggression, increased GAD65 expression and increased GABA neurons were observed in some brain areas of male hamsters given chronic AAS treatment (Grimes et al., 2003; Schwartzer et al., 2009) or repeated cocaine exposure during adolescence (Ricci et al., 2005). One explanation for the divergent findings of the effect of GABA on aggression may be that its actions depend on the brain area involved, the receptor types, and also the specific context of the situation responsible for evoking the aggressive behavior.

4.2.1 $GABA_A$ receptors—$GABA_A$ receptors are ligand-gated ion channels. The activation of $GABA_A$ receptors by the binding of GABA or corresponding agonists induces Cl^- influx into the cell and thus hyperpolarization of the surrounding membrane. The involvement of $GABA_A$ receptors in aggressive behavior seems to be well established, but the effect (either pro-aggressive or anti-aggressive) is quite intricate, possibly owing to the functional diversity that depends on the heterogeneous composition of receptor subunits.

More than 4 weeks of SI induces increased aggression in most male mice, male rats, and female hamsters (Wise, 1974; Simler et al., 1982; Toth et al., 2012). The decrease in $GABA_A$ receptor function caused by SI is possibly the result of reduced levels of the neurosteroid allopregnanolone, a positive allosteric modulator of $GABA_A$ receptors, in the frontal cortex, hippocampus and basolateral amygdala of male mice (Dong et al., 2001; Pinna et al., 2008; Nelson and Pinna, 2011). Fluoxetine treatment prevented decreases in level of allopregnanolone and reduced aggressive behavior in SI mice (Pinna et al., 2003). In addition, SI animals showed reduced sensitivity to $GABA_A$ receptor positive allosteric modulators such as barbiturates, neurosteroids and benzodiazepines (Matsumoto et al., 1999; Serra et al., 2000; Pinna et al., 2004). These studies consistently illustrate that the down-regulation of $GABA_A$ receptors via reduction of allopregnanolone is implicated in the escalated aggression induced by SI. In addition, mice that were selected for highly aggressive behavior showed decreased binding of benzodiazepines and also reduced $GABA_A$-dependent chloride uptake (Weerts et al., 1992). Thus, a reduction in $GABA_A$ receptor function may predispose individuals to initiate aggressive behaviors.

By contrast, agonists and positive allosteric modulators of the $GABA_A$ receptor have a range of effects on aggressive behavior, depending on dose, extending from inhibition to escalation (Puglisi-Allegra and Mandel, 1980; Miczek et al., 2003). Allosteric positive modulators such as benzodiazepines, alcohol, barbiturates, and neurosteroids enhance the inhibitory transmission of the $GABA_A$ receptor. Clinically, prototypical $GABA_A$-positive modulators have been used widely in the treatment of anxiety, convulsion, muscle tension,

and sleep disorders (Shader and Greenblatt, 1993). However, these drugs have so-called paradoxical effects, and acute administration of benzodiazepines may increase aggression in human patients, depending on the dose, the context, and the individual's history (Hall and Zisook, 1981; Dietch and Jennings, 1988; Bond et al., 1995).

Alcohol also acts as a positive allosteric modulator of $GABA_A$ receptors, and alcohol has been linked to violence and aggression in humans more frequently than any other drug (Miczek et al., 2002, 2004). The pro-aggressive effect of $GABA_A$ positive allosteric modulators has been confirmed in many rodent models. Benzodiazepines and some neurosteroids enhanced both inter-male aggression and maternal aggression in mice and rats (Miczek, 1974; Miczek and O'Donnell, 1980; Mos and Olivier,1989; Ferrari et al., 1997; Fish et al., 2001; Gourley et al., 2005). As shown in Figure 5, low to moderate doses of benzodiazepines enhanced inter-male aggressive behavior, but high doses of benzodiazepines inhibited aggression. Alcohol intake reliably escalates aggression in approximately 30% of male mice and rats, whereas the level of aggression in the other 70% either did not change, or decreased relative to their basal level after an administration of a moderate dose of alcohol (Miczek et al., 1992, 1998; van Erp and Miczek, 1997). This individual variation seems to be comparable to the human condition, and differences in the propensity for escalated aggression induced by alcohol may arise from functional and compositional differences in $GABA_A$ receptors. When alcohol is co-administered with allopregnanolone, animals that are vulnerable to the pro-aggressive effect of alcohol (alcohol-heightened aggression, AHA) and animals with alcohol-non-heightened aggression (ANA) respond to the treatment differently (Fish et al., 2001). Furthermore, pharmacological activation of $GABA_A$ receptors in the DRN enhances the pro-aggressive effect of alcohol, and animals with AHA are more sensitive to the $GABA_A$ receptor agonist muscimol than ANA animals (Takahashi et al., 2010a). However, intra-DRN injection of muscimol did not have any effect on aggression in non-drugged mice (Takahashi et al., 2010a), and even reduced inter-male aggression in rats (Van der Vegt et al., 2003).

The $GABA_A$ receptor is a pentameric receptor that comprises a combination of five subunits. There are seven main receptor subunit families (α, β, γ, δ, ε, θ, π), and some families have further isoforms (α1–6, β1–3, γ1–3). Benzodiazepines bind to a specific site formed by α and γ subunits; whereas $GABA_A$ receptors that contain either α1, α2, α3, or α5 are sensitive to benzodiazepines, $GABA_A$ receptors that contain α4 or α6 are not. The pharmacological properties of $GABA_A$ receptors vary, depending on the subunit composition (Mehta and Ticku, 1999; Tan et al., 2011). It has been proposed that the α2-containing $GABA_A$ receptors are responsible for the anxiolytic effect of benzodiazepine, whereas α1-containing $GABA_A$ receptors are involved in the sedative effect (Rudolph et al., 1999; Löw et al., 2000). The α1-containing $GABA_A$ receptors seem to play a key role in mediating the pro-aggressive effect of benzodiazepines. Antagonists such as βCCt and 3-PBC that act preferentially on α1-containing $GABA_A$ receptors reduced the aggression-heightening effects of midazolam or alcohol in mice and rats (De Almeida et al., 2004; Gourley et al., 2005). In addition, 4 weeks of SI alters the expression of $GABA_A$ receptor subunits, and male mice exposed to SI showed reduced α1 subunit expression in the hippocampus and PFC compared with group housed males (Pinna et al., 2006). Moreover, compared with group-housed males, SI males had reduced levels of the α2 and γ2 subunits

and increased levels of mRNAs that encode α4 and α5 subunits in the PFC (Pinna et al., 2006). Escalated aggressive behavior after benzodiazepine treatment is eliminated in mice with a point mutation of either the α1 or α2 subunit (Newman et al. unpublished). The attempt to dissect the role of each subunit of the $GABA_A$ receptor in the pro- and anti-aggressive effects of benzodiazepines is just beginning, and further investigation is required. Mice with a point mutation in the benzodiazepine binding site of a specific αsubunit and a knockout mouse for each subtype of $GABA_A$ receptor have been established (Rudolph and Knoflach, 2011), and these mice will facilitate analysis of the function of each of these subunit in controlling aggression.

4.2.2. $GABA_B$ receptor—The $GABA_B$ receptor is a metabotropic receptor, which mediates its effect less rapidly than the ionotropic $GABA_A$ receptor through the activation of Giα- or Goα-type G-proteins. The $GABA_B$ receptors are located on both pre- and postsynaptic terminals, and either suppress neurotransmitter release by inhibiting Ca^{2+} channels (presynaptic) or induce a slow inhibitory postsynaptic current (IPSC) through activation of inwardly rectifying K^+ channels (Bettler et al., 2004). Recently, the $GABA_B$ receptor has received increased attention because of its effect in several psychiatric diseases, such as anxiety, depression, and drug addiction (Cryan and Kaupmann, 2005; Cryan and Slattery, 2010; Vlachou and Markou, 2010), but the role of the $GABA_B$ receptor in aggressive behavior has not yet been examined fully. A clinical study found that oral administration of the $GABA_B$ receptor agonist baclofen inhibited provoked aggressive responses in subjects that had a history of childhood conduct disorder, whereas the same treatment escalated aggressive responses in control subjects in a laboratory setting (Cherek et al., 2002). In rats, baclofen also reduces escalated forms of aggressive-defensive behavior induced by electric shock, ethanol withdrawal, and apomorphine treatment (Rodgers and Depaulis, 1982; File et al., 1991; Rudissaar et al., 2000). In contrast, we found recently that systemic administration of baclofen showed an inverse U-shaped dose-effect on territorial aggressive behavior in male mice: low-to-moderate doses of baclofen increased aggressive behavior of male mice, whereas high doses of baclofen reduced aggressive behavior and were accompanied by motor incoordination (Takahashi et al., 2012). The DRN appears to be one of the sites targeted by baclofen, which would explain the aggression-escalating effect of baclofen. Intra-DRN administration of baclofen escalated inter-male aggressive behavior, and this pro-aggressive effect of baclofen extended across different strains of mice, such as C57BL/6J and outbred ICR or CFW strains (Takahashi et al., 2010c, 2012). The selective $GABA_B$ receptor antagonists phaclofen and CGP54626 both blocked this pro-aggressive effect of baclofen. *In vivo* microdialysis showed that $GABA_B$ receptor activation in the DRN increased the extracellular level of 5-HT in the mPFC (Takahashi et al., 2010c) (Figure 3). Thus, phasic activation of 5-HT neurons by indirect modulation of $GABA_B$ receptors may promote certain types of escalated aggressive behavior in mice.

5. Forward genetics of aggressive behavior in rodents

So far, we have seen several examples of gene knockout mice that are targeted at specific receptor subunits or molecules involved in intracellular cascades. These “gene driven” approaches, so-called *reverse* genetics, are useful when examining the effect of a specific gene on behavior. Deletion of any of more than 50 genes can either increase or decrease

aggressive behaviors in the mouse (Miczek et al., 2001; Takahashi et al., 2011). On the other hand, most behavioral phenotypes, including aggressive behavior, are known as "quantitative traits", and are attributable to multiple genes that have a subtle effect individually but have strong interactions with the environment as well as epistatic interactions among genes. *Forward* genetics is a top-down method that seeks to identify unknown genetic factors that contribute to individual differences in behavior. This section discusses attempts to identify the genetic basis of aggression using the forward genetics approach.

Inbred mouse strains have been widely used to examine the genetics of aggression (Ginsburg and Allee, 1942; Scott, 1942). For example, whereas the NZB/B1NJ strain shows extremely high inter-male aggression, the FVB/NtacfBR strain shows aggression toward females, and A/J mice rarely show any aggressive behavior even when they are reared in the same environment as aggressive strains (Canastar and Maxson, 2003; Roubertoux et al., 2005). In addition, these inbred strains respond differently to environmental factors such as past experiences of winning, defeat, or SI, suggesting that susceptibility to the environmental challenge is determined genetically (Ginsburg and Allee, 1942; Schneider et al., 1992). Selective breeding is another method used to examine the heritability of aggression. Highly aggressive and non-aggressive populations diverge promptly (in fewer than five generations) and, after several generations of artificial selection, these populations stabilize at high and low levels of aggressive behavior. The use of selective breeding to study inter-male aggression (Van Oortmerssen and Bakker, 1981), isolation-induced aggression (Lagerspetz, 1964; Cairns et al., 1983; Sandnabba, 1996) and maternal aggression (Gammie et al., 2006) in the mouse has indicated a genetic basis for these types of aggression. These lines selected for aggression have been accepted as good models of escalated aggression (Miczek et al. 2013). For example, the Short Attack Latency line (SAL) and the Long Attack Latency line (LAL) were originally developed from wild house mice that were bidirectionally selected on the basis of their latency to first attack (Van Oortmerssen and Bakker, 1981). In addition to shorter attack latency, SAL males also showed a "pathological" level of aggression manifested by heightened attack/threat ratios, attacks on vulnerable body parts of the opponent, and aggressive behavior toward females and anesthetized animals (De Boer et al., 2009; Natarajan et al., 2009).

Attempts have been made to identify quantitative trait loci (QTLs) that account for differences in levels of aggression between individuals which have been seen in the comparison of inbred strains and selected lines. In early studies, the involvement of chromosome (Chr) Y and Chr 17 of mice was examined because of the existence of the t haplotype on Chr 17 in the wild population and the comparatively easy establishment of Chr Y consomic strains (Miczek et al. (2001)). QTL analysis was undertaken for a genome-wide screen of genetic loci. QTL mapping is a statistical method to identify genetic loci that are linked to the phenotype, using the genetic polymorphisms between strains. To date, there have been only a few attempts to identify QTLs for aggressive behavior, possibly owing to the complexity of the behavior. Four QTLs, on Chr 5, Chr 10, Chr15 and Chr X, were identified by analyzing an F2 intercross between A/J mice and either NZB/B1NJ or BALB/c mice. Aggression was assessed by dangling an intruder by its tail at the corner of the cage

and examining the occurrence of aggressive attack by the resident male (Brodkin et al., 2002; Dow et al., 2011). QTL analysis has also revealed that inter-male aggression and isolation-induced aggression have different, as well as some overlapping, genetic contributions (Roubertoux et al., 2005).

Analysis of consomic strains (or Chromosome substitution strain) is another way to map the chromosomes that determine the level of aggression (Nadeau et al., 2000). Three panels of consomic mouse strains (Nadeau et al., 2000; Gregorova et al., 2008; Takada et al., 2008) and one panel for rats (Malek et al., 2006) are currently available. A consomic strain was made by replacing a single chromosome in a host strain with the corresponding chromosome from a donor strain. Since the mouse has 19 autosomes and X and Y sex chromosomes, a panel of consomic strain involves a total of 22 lines of inbred strains (Nadeau et al., 2000). In our laboratory, we use a consomic strain of the wild-derived mouse strain MSM/Ms and a common laboratory strain C57BL/6J (Takada et al., 2008). Male MSM mice are highly aggressive in the home cage and sometimes kill their littermates, and we found enhanced aggression in the consomic strains that have either Chr 4 or Chr 15 from MSM on the C57BL/6J background (Takahashi et al., 2010d; in preparation).

Identifying the novel genetic factors that contribute to individual differences in aggression is appealing because it will help to elucidate the neurobiological mechanisms responsible for aggression. However, we are far from confirming the actual causal gene within the QTL. Usually, a chromosomal region corresponding to the genetic locus identified by the QTL analysis contains several hundred genes. Also, it is not unusual for the genetic effect on behavior to be diluted, or disappear entirely, after the genetic locus has been narrowed down by production of a congenic mouse (Bryant et al., 2012). The difficulty in identifying the appropriate gene can possibly be attributed to the small effect of each QTL (less than 5%) as well as to complex epistatic interactions among genes (Flint et al., 2005; Manolio et al., 2009; Eichler et al., 2010).

The complexity of the genetic mechanisms of aggression also has to be considered when analyzing knockout mice. The deletion of one gene can have different effects depending on the genetic background. For example, the spontaneous mouse mutation *fierce* has deletion of the coding region of the Nr2e1 gene (tailless); both male and female *fierce* mice engage in extremely high level of aggressive behavior and are difficult to handle (Monaghan et al., 1997). However, the effect of the *fierce* mutation depends on the genetic background – mice with *fierce* on the C57BL/6J background are highly aggressive, whereas those with *fierce* on a mixed background of C57BL/6J and 129 only show intermediate levels of aggression. This background-dependent effect indicates a salient interaction between the deleted gene and other QTLs, so-called modifiers.

6. Concluding remarks

- Analysis of c-Fos expression has identified several brain areas that are implicated in inter-male aggression, maternal aggression, and escalated aggression. There are large overlaps among the brain areas that are involved in different types of aggression, but also some differentiation depending on the type of aggression.

- Electrical stimulation studies and optogenetic studies have shown that activation of the hypothalamus (hypothalamic attack area, HAA) induces pathological aggressive behavior in rodents. Arginine vasopression (AVP) modulates the activity of the hypothalamus and enhances aggressive behaviors in male rodents.
- The prefrontal cortex (PFC), especially the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC), have an inhibitory effect on aggression. 5-HT modulates the activity of the PFC, but its role in aggression depends on (1) the subtypes of receptors and the region of the brain in which they are expressed, and (2) the types of aggressive behaviors (species-typical aggression vs escalated aggression).
- The activity of the dorsal raphe nucleus (DRN), which sends dense 5-HT neuron projections into the PFC and other regions, is critical in aggression. The basal level of 5-HT (trait) and phasic change of 5-HT (state) have to be considered separately, and it is possible that they have different roles in aggressive behavior.
- Dopamine in the NAc increases during aggressive encounters, both in aggressors and defeated animals. Increased levels of dopamine in the NAc are also observed when an animal is anticipating an aggressive confrontation.
- Pheromonal information that is processed by the accessory olfactory bulb is essential for appropriate social behavior in rodents, including aggressive and sexual behaviors. Disrupting the activation of the vomeronasal organ (VNO) causes males to avoid aggressive behavior and show sexual behavior toward a male intruder.
- The balance between excitatory glutamate and inhibitory GABA is important in maintaining aggressive behavior at the species-typical (adaptive) level. Pharmacological and genetic studies have shown that almost all subtypes of glutamate (NMDA, AMPA, kainate receptors, and mGluRs) and GABA ($GABA_A$ and $GABA_{B)}$ receptors are involved in aggression. However, the role of each of the receptors may vary depending on the receptor subtype, its localization, and the type of aggressive behavior studied. Combinations of newly developed pharmacological agents that can manipulate a specific subtype of receptors and genetic models, such as conditional knockout or transgenic mice for a receptor subtype on the specific neurons, promise to elucidate the functions of these receptors in aggression.
- The forward genetics approach has successfully demonstrated the genetic contributions (QTLs) to aggression in the mouse. However, a breakthrough in methodology and technology is required to unravel the complicated interactions among genes and genetic backgrounds, and to understand the entire gene network that is involved in the individual differences in aggression.

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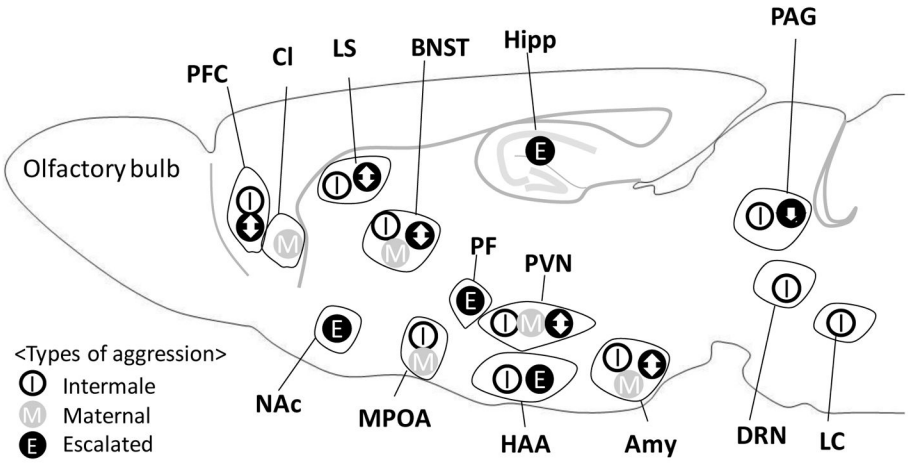

Figure 1.

Schemas of brain areas that are activated during and after an aggressive encounter. Observed by c-Fos immunohistochemistry. Open circles indicate intermale aggression; shaded circles, maternal aggression; and black circles, escalated aggression. An arrow in a circle indicates the area where the c-Fos activation was inhibited compared with intermale aggression (downwards arrow) or mixed reports, depending on the study (bidirectional arrow). Prefrontal cortex (PFC), claustrum (Cl), lateral septal nucleus (LS), bed nucleus of the stria terminals (BNST), nucleus accumbens (NAc), piriform cortex (Pir), medial preoptic area (MPOA), paraventricular nucleus (PVN), parafacicular nucleus of thalamus (PF), hypothalamus attack areas (HAA), amygdala (Amy), hippocampus (Hipp), periaqueductal gray (PAG), 5-HT neurons in the dorsal raphe nucleus (DRN), and locus coeruleus (LC). In this figure, HAA includes the anterior, ventromedial and lateral hypothalamic nuclei. (Kollack-Walker and Newman, 1995; Joppa et al., 1995; Potegal et al., 1996; Wang et al., 1997, 2011; Delville et al., 2000; Gammie and Nelson, 2001; Halász et al., 2002, 2006; van der Vegt et al., 2003; Davis and Marler, 2004; Haller et al., 2005b, 2006; Veening et al., 2005; Gobrogge et al., 2007; Pan et al., 2010; Nehrenberg et al., 2012; Wall et al., 2012; Konoshenko et al., 2013)

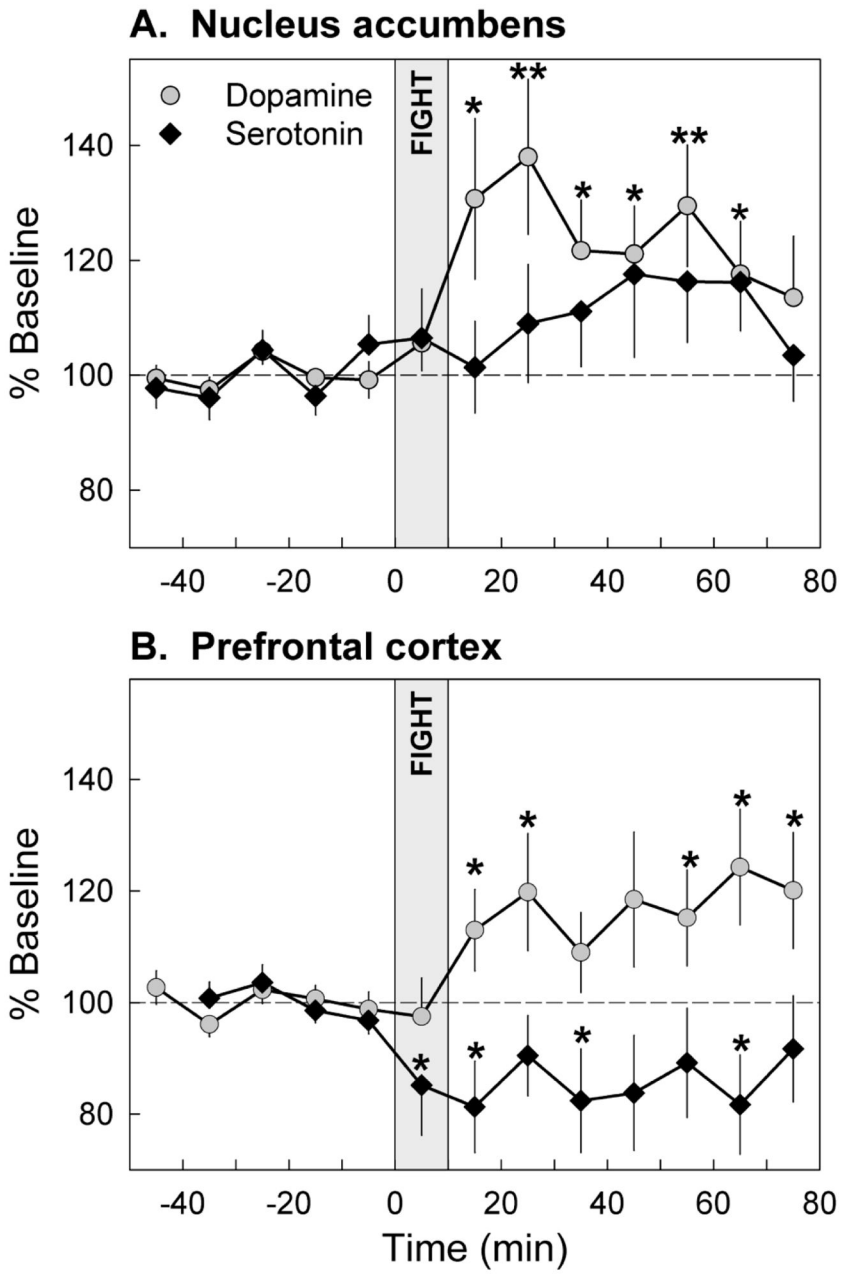

Figure 2.

Changes of dopamine and serotonin in the PFC and NAc during species-typical aggressive behavior in the rat. 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 increased after the confrontation, while serotonin levels did not change significantly. (b) In the prefrontal cortex (bottom panel), dopamine levels increased after the confrontation, whereas serotonin decreased after the confrontation. The vertical light gray bar indicates the occurrence of the 10-minute fight. * $p<0.05$ and ** $p<0.01$ compared with baseline. Reprinted with permission from Van Erp and Miczek (2000).

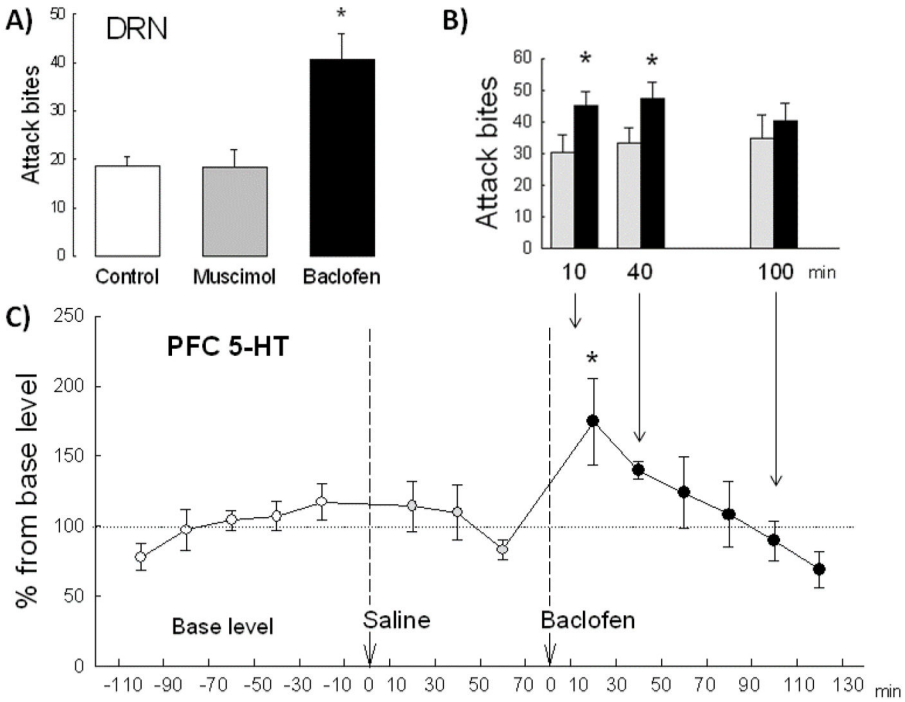

Figure 3.

Modulation of the dorsal raphe nucleus (DRN) by GABA receptors and escalated aggression in the mouse. (A) Microinjection of the $GABA_B$ receptor agonist baclofen into the DRN increased intermale aggressive behavior, whereas microinjection of the $GABA_A$ receptor agonist muscimol into the DRN did not have any effect. (B) Temporal change in the effect of 0.06 nmol baclofen on attack bites. Escalated attack bites were observed both 10 and 40 minutes after the intra-DRN baclofen injection, and return to basal level after 100 minutes. (C) Extracellular serotonin (5-HT) concentration in the medial prefrontal cortex (mPFC) of mice after intra-DRN baclofen injection. Baclofen increased 5-HT release in the mPFC whereas saline injection did not change the level of 5-HT. Data are expressed as percentage of baseline (n=7). * $p<0.05$ compared with the vehicle control (A and B) or baseline (C). Adopted from Takahashi et al. (2010).

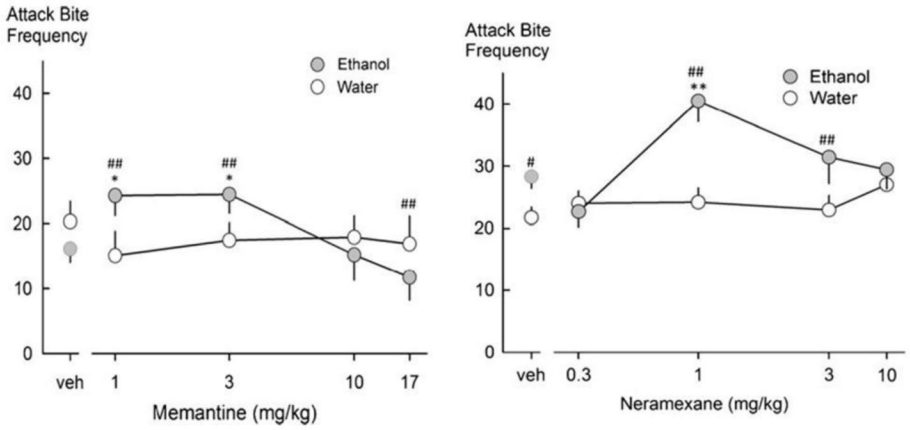

Figure 4.

Systemic administrations of non-competitive NMDA receptor antagonists enhance aggressive behavior specifically when associated with the administration of alcohol. Frequencies of attack bites following self-administration of either water or ethanol (1g/kg) combined with either memantine (left panel) or neramexane (right panel) treatment. *$p < 0.05$, **$p < 0.001$ compared with vehicle; #$p < 0.05$, ##$p < 0.001$ ethanol compared with water. Reprinted with permission from Newman et al. (2012).

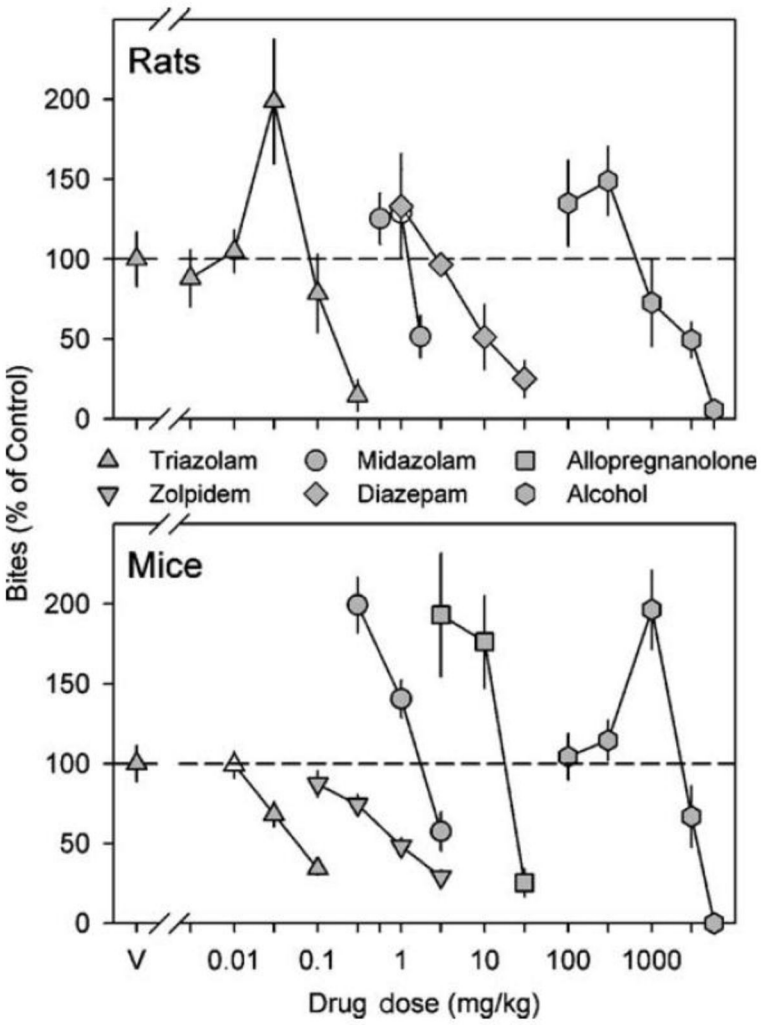

Figure 5.

$GABA_A$-positive allosteric modulators and aggression. Biphasic effects of $GABA_A$ receptor-positive modulators on aggression in rats (top panel) and mice (bottom panel). Low doses of alcohol, the benzodiazepines diazepam (rats only) and midazolam and the neurosteroid allopregnanolone (mice only) increase the frequencies of attack bites, expressed as a percentage of vehicle control, whereas higher doses decrease this measure of aggression. Triazolam increases attack bites in rats but not mice. No increase in aggression was seen after treatment with zolpidem, a alpha1 receptor selective agonist (tested for mice only). The dotted line represents the baseline at 100%. Reprinted with permission from Miczek et al. (2007).

Table 1

Types of aggressive behavior in rodent models

A) Species-typical aggression			
	Definition	**Test situation or Experimental variable**	**Reference**
Territorial aggression (intermale aggression)	The behavior of a male in control of an "exclusive territory". A breeding male resident rodent threatens and attacks an adult male that intrudes into the territory.	Resident-intruder test in the established territory. In the laboratory, the experimental male (*resident*) is pair-housed with a female. A male stimulus animal (*intruder*), which has been group-housed with other males is introduced into resident's cage. Both the frequency and duration of both aggressive behaviors (e.g. attack bites, pursuit, and sideways threat) and non-aggressive behaviors (e.g. walking, rearing, and self-grooming), and the latency to the first bite are recorded by human observation.	Crawley et al., 1975; Murphy, 1976; Miczek and O'Donnell, 1978
Dominance	The behavior of one male who dominates others. Dominance hierarchy is common in rats but group-housed male C57BL/6 mice also show hierarchy.	Observation of the agonistic and submissive behaviors in the group housed home-cage. Also, in mice, the tube test can be used to evaluate social dominance. In this test, two mice are released into the opposite ends of a narrow tube. The expectation is that the dominant male forces the opponent forward and out of the tube.	Popova and Naumenko, 1972; Blanchard and Blanchard, 1977; Wang et al., 2011
Maternal aggression	Aggressive behavior expressed by females shortly before gestation, which reaches a peak during the first week postpartum, and declines thereafter.	Resident-intruder test in the home-cage of lactating females from postpartum day 1 to 7. Either a male or female intruder is introduced into dam's cage. In addition to the variables observed for territorial aggression in the male, attack bites directed at the snout and the face can be observed.	Noirot et al., 1975; Hurst, 1987; Haney et al., 1989; Lonstein and Gammie, 2002; Sgoifo et al., 2006
Female aggression	Aggressive behavior expressed by females to compete for reproductive opportunities.	Female rats pair-housed with a breeding male. Resident- intruder test using sexually matured female as an intruder. In the hamster, females show male-like territorial behavior toward both male and female intruders.	Payne and Swanson, 1970; DeBold and Miczek, 1981; Bowler et al., 2002
Pair-bonding induced aggression	Monogamous prairie voles show exclusive aggressive behavior toward intruders once they form pair bonds with a female.	Within 24 h of mating with a female, the sexually-experienced male prairie vole attacks conspecific intruders of both sexes and exhibits affiliative behaviors only towards his mate.	Insel et al., 1995

B) Escalated aggression			
	Definition	**Test situation and Experimental design**	**Reference**
Social provocations (social instigation)	The presence of a breeding male provokes the resident into intense and frequent aggressive behavior, when given the opportunity. It is likely that the olfactory, visual, and auditory cues emanating from the intruder induce "aggressive arousal" or "attack readiness" in the resident male.	A resident male is exposed to another breeding male (instigator) in his home-cage without direct agonistic interaction. The instigator is behind a protective screen, and thus the resident male can see, smell, and hear the instigator male. Immediately after the provocation, an intruder male which is different from the instigator is introduced into the home-cage of the resident male.	Heiligenberg, 1974; Potegal and Tenbrink, 1984; Potegal, 1991; Fish et al., 1999
Social isolation (SI)	Social isolation induces higher levels of attack on the background of increased defensiveness.	Males isolated for at least 4 weeks prior to resident-intruder encounter.	Guidotti et al., 2001; Töth et al., 2008
Alcohol-heightened aggression (AHA)	A subset of mice and rats (ca. 30%) show escalated aggressive behavior after the consumption of alcohol compared to their base-line aggression (aggressive behavior after water consumption).	Animals receive ethanol (1.0g/kg) orally 15 minutes before the resident-intruder encounter. Water access is restricted for 21 hours before the test. Operant conditioning is used to allow the animal to self-administer a certain amount of ethanol.	Blanchard et al., 1987; Miczek et al., 1992, 1998; Miczek and de Almeida, 2001

B) Escalated aggression			
	Definition	**Test situation and Experimental design**	**Reference**
Hypoglucocorticoid status (ADXr)	Surgery and replacement of a low level of glucocorticoid escalates aggressive behavior in the male rats. ADXr animals provide a model of hypoarousal aggression owing to their low heart rates during aggressive encounters.	Animals are adrenalectomized and implanted with a low corticosterone pellet (ADXr). Escalation of aggression is observed 1 week after the surgery.	Haller et al., 2001, 2004
Chronic anabolic-androgenic steroids (AAS)	Exposure to chronic anabolic-androgenic steroids during adolescence predisposes male hamsters and rats to escalate aggressive behavior.	Animals are treated with a cocktail of anabolic-androgenic steroids (AAS) by subcutaneous injections daily for 30 consecutive days during puberty.	Melloni et al., 1997
Artificial selection on aggression	Genetic model to examine the heritability of aggressive behavior. Selective breeding has successfully produced highly aggressive lines for intermale aggression, isolation-induced aggression, and maternal aggression in the mouse.	Breeding of highly aggressive individuals in the population to produce the next generation. Characterization of aggressive behavior of all offspring is performed every generation, and the highly aggressive individuals are selected each generation.	Van Oortmerssen and Bakker, 1981; Cairns et al., 1983; Sandnabba, 1996; Gammie et al., 2006