Animal Models of Aggression

The Role of Sex and Social Experience

Vinícius Elias de Moura Oliveira

Contents

Abstract

Rodent models have been extensively used to study the neural underpinnings of aggression. Yet, the role of some external factors such as social experiences, or internal factors such as biological sex, have only recently gained attention. This chapter discusses how the composition of the social environment and/or the lack of social contact (social isolation) in different stages of development impact the display of aggressive behavior in rodents. Additionally, this chapter covers how biological sex interacts with changes in the composition of the social environment to affect the neuronal networks of aggression. From a neurobiological point of view, this chapter focuses particularly on the participation of neuroendocrine systems such as sex hormones, oxytocin, and vasopressin and on how social interactions shape brain plasticity within those systems.

V. E. d. M. Oliveira (✉)
Laboratory of Neuroendocrinology, GIGA-Neurosciences, University of Liege, Liege, Belgium
e-mail: vedmoliveira@uliege.be

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Aggression · Social interactions · Social experience · Mating · Winner effect · Neuronal plasticity · Social isolation · Oxytocin · Vasopressin · Sex hormones · Estrogen receptor α · Lateral septum · Nucleus accumbens · Ventromedial hypothalamus

Abbreviations

AH	Anterior hypothalamus
AVP	Vasopressin
BDNF	Brain-derived neurotrophic factor
BLA	Basolateral amygdala
BNST	Bed nucleus of stria terminalis
CCKA	Cholecystokinin receptor A
CeA	Central amygdala
CSF	Cerebrospinal fluid
DG	Dentate gyrus
dLS	Dorsal lateral septum
DMH	Dorsomedial hypothalamus
DR1	Dopamine receptor 1
DR2	Dopamine receptor 2
EPCs	Excitatory postsynaptic currents
Erα	Estrogen receptor alpha
FMRP	Fragile X mental retardation protein
GH	Group-housed
HAA	Hypothalamic attack area (mediobasal hypothalamus)
IL	Infralimbic cortex
IST	Isolated and trained
LH	Lateral hypothalamus
LS	Lateral septum
LTD	Long-term depression
LTP	Long-term potentiation
MeA	Medial amygdala
MeApv	Medial amygdala posteroventral
mGluR5	Metabotropic glutamate receptor 5
MPOA	Medial preoptic area
Nacc	Nucleus accumbens
NK3R	Neuorkinin receptor 3
NKB	Neurokinin B
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NPY2	Neuropeptide Y receptor 2
OF	Orbitofrontal cortex
OXT	Oxytocin

OXTR	Oxytocin receptor
PAG	Periaqueductal gray matter
PFC	Prefrontal cortex
PR	Progesterone receptor
PrL	Prelimbic cortex
PVN	Paraventricular nucleus of the hypothalamus
PWSI	Postweaning social isolation
RIT	Resident Intruder Test
SI	Social Isolation
SON	Supraoptic nucleus of the hypothalamus
TAC2	Tachykinin 2
V1aR	Vasopressin 1a receptor
vLS	Ventral lateral septum
VMHvl	Ventrolateral ventromedial hypothalamus
VTA	Ventral tegmental area

Introduction

Social interactions shape our day-to-day life. Experiences such as going out with friends, having sex, being bullied, or winning a fight may affect one's behavior and/or emotional state. Additionally, the lack of social contact might elicit emotional distress and antisocial behaviors as seen during the social deprivation imposed by the COVID-19 pandemic (de Figueiredo et al. 2021; Kim and Jung 2021; Mojahed et al. 2021).

Animal behavior is also influenced by the composition of the social environment as multiple factors such as engaging in sexual activity, winning agonistic conflicts, social defeat, or lack of social interactions (social isolation, SI) are known to alter animals' physiology and behavior (for a review, please see [Hsu et al. 2006; Masis-Calvo et al. 2018; Menon et al. 2018; Oliveira et al. 2022a; Remedios et al. 2017; Sandi and Haller 2015; Waldherr and Neumann 2007]).

Of note, one of the behaviors strongly affected by disruptions of social systems is aggressive behavior. Although aggression has been described as an innate and hardwired behavior, several studies have pointed out that positive and negative social interactions such as mating (Koolhaas et al. 1980, 2013; E. L. Newman et al. 2019; Remedios et al. 2017), social isolation (Oliveira et al. 2019, 2021; Ross et al. 2019; Toth et al. 2011; Trainor et al. 2007; Zelikowsky et al. 2018), and successive aggressive interactions (Been et al. 2016; Chase et al. 1994; Nordman et al. 2020; Oliveira et al. 2021; Stagkourakis et al. 2020) might influence the animal's natural tendency to aggress. In fact, social isolation, cohousing (mating), and aggression training have been used to instigate and/or escalate the levels of aggression displayed by rodents for years (Haller 2013; Koolhaas et al. 1980, 2013; Miczek et al. 2001, 2013; Sandi and Haller 2015).

Here the behavioral responses and neural mechanisms underlying social experience-mediated facilitation of aggression will be described. Particular focus

will be given to the effect of mating, aggressive training, and SI on aggressive behaviors. Additionally, as the neurobiological mechanisms regulating aggression in females have been poorly described in rodents a parallel between males and females will be drawn when pertinent.

Mating and Aggression

Classically, cohousing a sexually mature male with a sexually receptive female has been described as an efficient paradigm to establish territoriality and trigger aggressive behavior in several rodent species (Gubernick and Alberts 1987; Koolhaas et al. 1980, 2013; Miczek et al. 2001; Terwilliger and Young 2014). In detail, this protocol is based on the principle that males will generally exhibit a polygynous reproductive strategy, attempting to copulate with as many females as possible to achieve reproductive fitness. Thus, dominant males will display high levels of aggression toward their potential "rivals" to protect their mate (Campbell 1999; Hashikawa et al. 2018; Koolhaas et al. 1980; Lischinsky and Lin 2020; Miczek et al. 2001; Nelson and Trainor 2007). In the resident intruder test (RIT), an unknown sexually mature but slightest smaller (10–20% of the resident's body weight) male intruder is inserted in the resident's (mated male) cage. Typically, the presence of this "rival" in the resident's cage will elicit high levels of aggressive behavior even though the resident's mate (receptive female) is removed from the home cage. Additionally, this behavior persists for long periods of time even in the absence of the female; this suggests that mating itself triggers some type of plastic modifications in the rodent's brain and physiology to facilitate the display of aggressive behaviors (Koolhaas et al. 2013).

In females, the effects of mating on aggression have been less studied. However, mating and cohabitation with a male seem to also stimulate female aggression; for a detailed review, please see (Oliveira and Bakker 2022). In socially monogamous species such as California mice and prairie voles, mating followed by the establishment of a pair bond enhances aggression toward female intruders (Bowler et al. 2002; Gubernick and Alberts 1987; Karelina et al. 2010; Oliveira and Bakker 2022). Similarly, in mice (Aubry et al. 2022b; E. L. Newman et al. 2019) and rats (Ho et al. 2001) mating and cohabitation with a gonadectomized or sterilized male also triggers exacerbated levels of female aggression.

Altogether, this data implies that the display of sexual behavior affects the neurocircuitry involved in aggressive behavior facilitating behavioral responses. The next section discusses the potential neuro- and hormonal mechanisms underlying this phenomenon.

Neurobiological Mechanisms

The neural circuits regulating fighting and mating are highly conserved across species and share important hubs with one another (Lenschow and Lima 2020;

Lischinsky and Lin 2020; Wei et al. 2021; Yamaguchi 2022). Those are mostly the regions integrated into the so-called social behavior network, a cluster of brain areas expressing sex hormone receptors such as estrogen receptor alpha (ERα), and indirectly or directly receiving sensorial input from the olfactory system (S. W. Newman 1999). Regions such as the medial preoptic area (MPOA), the ventrolateral portion of the ventromedial nucleus of the hypothalamus (VMHvl), the anterior hypothalamic area (AH), the bed nucleus of stria terminalis (BNST), the lateral septum (LS), the medial amygdala (MeA), and the midbrain have been shown to regulate multiple social behaviors including mating and aggression (Nelson and Trainor 2007; S. W. Newman 1999). Although the networks involved in mating and aggression overlap to a high extent, the neuronal mechanisms by which those pathways interact remain largely unknown.

Interestingly, ERα-expressing neurons in the VMHvl (Lee et al. 2014) and BNST (Bayless et al. 2019; B. Yang et al. 2022a) have been shown to modulate both sexual and aggressive behaviors in male mice. Thus, one could hypothesize that the same neuronal population will regulate both behavioral outputs, thereby mating could potentially enhance aggressive behavior in males by "sensitizing" neurons involved in aggression. In fact, VMHvl-ERα^{+} neurons are known to exhibit a scalable control of social behaviors, meaning that a low activity of ERα^{+} neurons elicits mating whereas a high activity of those neurons leads to fighting (Lee et al. 2014). As cohabitation with a female is known to elevate testosterone levels in the plasma of males (Koolhaas et al. 1980), one could predict that increased testosterone might be converted into estradiol in the brain, via the rich MeA-aromatase projections innervating the VMHvl of male mice (Wu et al. 2009). This newly synthesized neuroestradiol could act as a potential factor priming the VMHvl-ERα+ neurons and subsequently eliciting aggression.

Although this mechanistic explanation seems appealing, previous results have shown that sexual activity changes the representation of intruder sex in the VMHvl-ERα neuronal populations. In detail, in inexperienced males, those neuronal assemblies are activated by intruders of both sexes whereas in breeders (experienced males) the overlap between male- and female-activated neuronal assemblies is reduced (Remedios et al. 2017). Importantly, those divergent clusters could still impinge on each other to facilitate fighting behavior, via collateral glutamatergic projections; further studies should dissect microcircuits within the VMHvl-ERα population.

A similar mechanism is unlikely in females as different neuronal populations regulate sexual and aggressive behavior in the VMHvl (Hashikawa et al. 2017). In fact, previous studies have shown a topographical and cell-specific control of mating and aggression in the female VMHvl (Oliveira and Bakker 2022). Briefly, aggression cells (expressing NPY2 receptor, β cells) are in the medial part of the VMHvl (Liu et al. 2022) whereas mating cells (expressing CCKA receptor, α cells) are located laterally in the VMHvl (Yin et al. 2022). Importantly, those populations are known to inhibit each other's behavioral output thereby sensitization is unlikely.

Another potential mechanism by which mating might increase aggressive behavior in males is via recruiting the reward system. Both aggressive (Beiderbeck et al. 2012; Dai et al. 2022) and sexual behavior (Dai et al. 2022) are known to trigger dopamine release in the ventral tegmental area (VTA) – nucleus accumbens (NAcc) pathway in males. Conversely, in females, dopamine release in the NAcc was absent during maternal aggression and was lower than in males during the consummatory phase of sexual behavior (Dai et al. 2022). This suggests that either i) females do not find aggression rewarding and/or reinforcing or ii) females use a different neurotransmitter and/or neuromodulatory system to establish their mating and/or aggression reward. In fact, a recent study has demonstrated that in contrast to males, females do not perceive aggression as reinforcing and/or rewarding. Specifically, cohoused female mice did show aggression-seeking behavior in the aggression-conditioned place preference and aggression-operant self-administration test (Aubry et al. 2022b).

Male mice, on the other hand, are known to develop aggression-seeking and addiction-like aggressive behavior (Aleyasin et al. 2018; Aubry et al. 2022a; Falkner et al. 2016; Golden et al. 2017, 2019). Thus, in theory, mating-induced dopamine release could prime or generate plasticity in dopamine receptor (DR)-positive and aggression-activated cells in the NAcc. In fact, both dopamine receptors 1 (DR1) and 2 (DR2) seem to contribute to the display of aggressive behavior in males (Beiderbeck et al. 2012; Golden et al. 2019). Future studies should elucidate how dopamine release in the mesolimbic pathway might affect aggression-sensitive neurons in the NAcc.

A potential factor by which mating might stimulate female aggression is the neuropeptide oxytocin (OXT). OXT signaling has been associated with prosocial and antiaggressive effects in males (Calcagnoli et al. 2013; de Jong and Neumann 2017; Lukas and de Jong 2017; Masis-Calvo et al. 2018). However, in females, OXT has been reported to facilitate aggression in virgin and lactating rodents (Bosch 2013; Bosch et al. 2004, 2005; Oliveira and Bakker 2022; Oliveira et al. 2019, 2021, 2022b). As sexual activity is known to trigger OXT release in the paraventricular nucleus of the hypothalamus (PVN) (Nyuyki et al. 2011), one could hypothesize that increased OXT release after mating would act in OXT-responsive neurons involved in virgin female aggression such as GABAergic neurons in the ventral lateral septum (vLS) (Oliveira et al. 2021) and central amygdala (CeA) (Oliveira et al. 2022b) to escalate aggression. Additionally, during lactation OXT has been described to self-prime its own release by acting on OXT receptors (OXTRs) in the supraoptic nucleus of the hypothalamus (SON) to trigger somatodendritic OXT release (Ludwig and Leng 2006); similar mechanisms have been described recently in the PVN (Qian et al. 2023). One could hypothesize that mating-related OXT release might prime OXT neurons in the PVN and/or SON to elevate aggression-related release and, consequently, facilitate female aggression. Future studies should focus on how sexual activity affects OXT neurons' activity and release during other social behaviors, including aggression.

Aggression "Priming" (Aggression Training: Winner Effect)

Engaging and winning successive aggressive interactions is a known paradigm to exacerbate aggressive behavior, the so-called *winner effect* or *aggression priming* (Chase et al. 1994; Hsu et al. 2006). This is a highly conserved phenomenon observed across several taxa from insects to mammals (Chase et al. 1994; Hsu et al. 2006; Otroen 1990; Oyegbile and Marler 2005; Schuett 1997). In humans, similar behavioral patterns have been described in recidivist perpetrators (Reidy et al. 2013, 2015; Sumner et al. 2015).

The winner effect has been extensively documented in male rodents, and although the number of encounters and the behavioral output (number of attacks, attack latency, and the percentage of time spent on aggression) may differ across studies, one thing is certain the successive winning and/or exposition to aggression increases the promptness of an animal to attack as well as the probability of winning (De Almeida et al. 2005; Miczek et al. 2013; Nordman et al. 2020; Oyegbile and Marler 2005; Staffend and Meisel 2012; Stagkourakis et al. 2020; Veenema et al. 2010). Importantly, only a few studies have attempted to describe how fighting experience and subsequent winning may affect aggressive behavior and neurobiology in females (Been et al. 2016, 2019; Oliveira and Bakker 2022; Oliveira et al. 2021; Silva et al. 2010).

In the next section, I will examine the neurobiological mechanisms controlling the winning-mediated enhancement of aggressive behavior in both sexes.

Neurobiological Mechanisms

A couple of papers have investigated the neurobiological and plastic changes underlying the winning enhancement of aggression in mice. Most of those studies have been focused on males and in the VMHvl as this region has been shown to be crucial for the display of male aggression in mice (Lee et al. 2014; Lin et al. 2011; C. F. Yang et al. 2013). Additionally, other studies have investigated how winning experiences affect plasticity in the NAcc of female hamsters (Been et al. 2016, 2019; Staffend and Meisel 2012) and neuropeptide release in rats (Oliveira and Bakker 2022; Oliveira et al. 2021).

In hamsters, successive winning experience was associated with escalated aggression (shorter attack latencies and higher number of attacks), those behavioral changes were accompanied by increased dendritic spines density in the NAcc (Staffend and Meisel 2012). The molecular mechanism underlying those morphological changes was further dissected in females. Briefly, aggressive experience transiently decreases Fragile X Mental Retardation Protein (FMRP) phosphorylation; this was associated with a long-lasting increase in the expression of scaffolding synaptic proteins PSD-94 and SAPAP-3. Furthermore, the blockade of excitatory inputs via the administration of metabotropic glutamate receptor 5 (mGluR5)

antagonist suppressed aggressive behavior escalation and molecular changes (Been et al. 2016, 2019).

In virgin female rats, successive fighting was associated with alterations in the vasopressin (AVP) and OXT systems. The release of both peptides has been strongly associated with aggressive and social behavior in both sexes (Lukas and de Jong 2017; Masis-Calvo et al. 2018; Oliveira and Bakker 2022). Briefly, in isolated female rats, aggression training, consisting of three consecutive aggressive interactions with a same-sex intruder, enhanced the percentage of time spent on aggression as well as the percentage of time and frequency of attacks (Oliveira et al. 2021, 2022b). Those behavioral changes were associated with elevated OXTR binding in the CeA (Oliveira et al. 2022b) and decreased OXTR and vasopressin 1a receptor (V1aR) binding in the ventral (vLS) and dorsal (dLS) LS (Oliveira et al. 2021), respectively. Of note, in all regions studied, differences in receptor binding were followed by changes in GABAergic neuronal activity (Oliveira et al. 2021, 2022b). Particularly in the LS, alterations in GABAergic transmission are causally linked with exaggerated aggression (Oliveira et al. 2021).

Regarding peptide release, social isolation and aggressive experience were shown to increase OXT content in the CSF of virgin females. Surprisingly, OXT levels were correlated with aggressive behavior intensity, meaning that high OXT levels were seen in highly aggressive females. Those differences in peptide content were mirrored locally in the LS, where heightened OXT release was found. Of note, experiments aiming to boost the OXT signaling and/or release either using pharmacology or viral tools (chemo- and optogenetics) mimicked the effects of social isolation and aggression training (IST) in naive females. Accordingly, the blockade of OXTRs, via OXTR antagonist, decreased aggression in IST female rats (Oliveira et al. 2021) (Fig. 3).

In contrast with OXT, AVP content was reduced exclusively in the CSF of IST females after an aggressive encounter. This was also reflected locally in the LS, as highly aggressive IST rats showed reduced AVP release compared to group-housed (GH) females during a social encounter. Accordingly, pharmacologically enhancing AVP signaling strongly reduced female aggression in IST rats whereas blockade of V1aRs exacerbated aggression in GH females (Oliveira et al. 2021). Of note, OXT release seems to respond to both social isolation and aggression training whereas AVP content and release were altered exclusively by aggression training (Oliveira et al. 2021). These data indicate that aggressive experiences particularly affect the AVP system of females; interestingly, AVP is known to influence GABAergic synaptic transmission and inhibitory circuits suppressing aggression in both sexes (Allaman-Exertier et al. 2007; Leroy et al. 2018; Oliveira et al. 2021; Raggenbass et al. 1987). Thus, one could hypothesize that AVP acts as a gateway, filtering inhibitory inputs in order to trigger appropriate behavioral responses. In fact, similar findings have been suggested in the olfactory system in response to social stimuli (Lukas et al. 2019; Suyama et al. 2021; Tobin et al. 2010) (Fig. 3).

The neuroendocrine mechanisms regulating aggression priming have been described more extensively in male mice. Successive winning was shown to increase plasma testosterone concentration in male mice (Oyegbile and Marler 2005;

Stagkourakis et al. 2020). Regarding neurobiological mechanisms, aggression priming was reported to be dependent on the activation of glutamatergic neurons in the posteroventral MeA (MeApv), as optogenetic stimulation and inhibition of those neurons were shown to block and induce escalated aggressive behavior in mice, respectively. Additionally, the effects of aggression priming on aggressive behavior were modulated by NMDAR-dependent potentiation of the MeApv. In detail, long-term potentiation (LTP) of MeApv projections to the BNST and VMHvl is necessary to induce exaggerated aggression in primed mice (Nordman et al. 2020).

A recent study has further dissected those plasticity-mediated mechanisms in the VMHvl. Stagkourakis and coauthors have shown that aggression training particularly affects the VMHvl-ERα^{+} neurons. In contrast to nonaggressors (exposed to multiple RITs without developing escalated aggression), aggressors show higher levels of plasma testosterone as well as increased spine density, and excitatory postsynaptic current (EPCs) frequency in VMHvl-ERα+ neurons. Additionally, aggressors' VMHvl-ERα neurons exhibited long-lasting LTP compared to non-aggressor. Interestingly although both groups showed long-term depression (LTD), nonaggressor exihibited higher LTD amplitude. Accordingly, inducing LTP or LTD, in vivo, via optogenetic stimulation induced (even toward heavier intruders) or inhibited exaggerated aggression, respectively. Finally, the authors elucidate the mechanisms driving synaptic plasticity and heightened aggression in those animals. Briefly, they found that treating nonaggressors with testosterone for 7 days enhances LTP in vivo as well as aggressive behavior display (attack duration and frequencies). All in all, this study demonstrates that aggression training generates exaggerated aggression as well as synaptic plasticity in the VMHvl-ERα neurons via increasing plasma concentrations of testosterone in male mice (Stagkourakis et al. 2020). Yet, the mechanism regulating elevated testosterone remains elusive (Fig. 2).

Social Isolation and Aggressive Behavior

As mentioned before, the composition of the social environment and the establishment of healthy social interactions strongly impact one's behavior and brain function (de Figueiredo et al. 2021; Kim and Jung 2021; Masis-Calvo et al. 2018; Mojahed et al. 2021; Sandi and Haller 2015).

Social deprivation either early in life (from puberty to adulthood) or during adulthood strongly affects aggressive behavior displayed by rodents (Borland et al. 2019; Elliott Albers et al. 2006; Miczek et al. 2013; Oliveira et al. 2019, 2021; Ross et al. 2019; Toth et al. 2011; Zelikowsky et al. 2018). This chapter focuses on how social isolation affects neurobiology and aggressive behavior in rodent animal models.

Postweaning social isolation (PWSI) induces exaggerated aggression in male and female Wistar rats (Oliveira et al. 2019; Toth et al. 2011). Although both sexes exhibited increased aggressive behavior toward a same-sex conspecific, characterized by longer time spent on total aggression and threat as well as short attack latencies and a higher number of attacks (Oliveira et al. 2019), abnormal aggression

was displayed in a sex-specific manner (Haller 2013). Particularly, males tended to show a higher number of attacks as well as a higher attack frequency toward vulnerable targets (e.g., throat, belly, paws, and neck of intruders) whereas females showed a higher percentage of time displaying aggressive behavior toward a juvenile intruder (Oliveira et al. 2019). The ethological and neurobiological mechanisms regulating this sex-specific display of abnormal aggression remain unknown.

Of note, in males, resocialization for 3 weeks after PWSI was able to rescue disrupted prosocial behaviors such as nonaggressive social interactions and decreased number of bites. However, abnormal aggression characterized by an increased number of attacks toward vulnerable targets was sustained even after resocialization (Tulogdi et al. 2014). Taken together, these results suggest that the neural alterations underlying this pathological aggressive behavior in PWSI rats are permanent and cannot be reversed by social housing after this plastic window between weaning and adulthood (Sandi and Haller 2015). The next section discusses the biological mechanisms underlying those behavioral changes.

In adults, social isolation has been also reported to enhance aggression in several male rodent species such as wild and lab mice, rats, and hamsters (Borland et al. 2019; Elliott Albers et al. 2006; Koolhaas et al. 2013; Miczek et al. 2001, 2013; Ross et al. 2019; Yang et al. 2022b; Zelikowsky et al. 2018). In adult females, the effects of social isolation on aggressive behavior have been less studied (Oliveira and Bakker 2022). Nevertheless, social deprivation has been reported to enhance virgin female aggression in CD1 Swiss Webster mice (Hashikawa et al. 2017), hamsters (Borland et al. 2019; Ross et al. 2019), California mice (Silva et al. 2010; Trainor et al. 2010), and Wistar rats (Oliveira et al. 2021, 2022b). For a detailed review of rodent models to study "rivalry" aggression in females, please see (Oliveira and Bakker 2022).

Early-Life Social Isolation Neurobiological Mechanisms

The effects of PWSI in males have been extensively characterized over the last few years. From an autonomic and neuroendocrine perspective, PWSI induces increased corticosterone and heart rate in response to an aggressive encounter, characterizing a hyperarousal type of aggression (Toth et al. 2011). Regarding the social neuropeptide OXT, PWSI was found to increase OXT mRNA in the PVN of isolated animals, regardless of sex. This was followed by decreased OXTR binding in the NAcc of isolated rats of both sexes. AVP mRNA levels were not changed in PWSI. However, V1aR binding was reduced in the dentate gyrus (DG) and the lateral hypothalamus (LH) of socially deprived rats, independent of sex. In the anterior BNST, V1aR binding was changed in a sex-specific manner, and receptor binding was reduced in females whereas increased in males after PWSI (Oliveira et al. 2019) (Fig. 1).

Concerning neural activity (c-FOS), fighting was found to recruit multiple brain regions embedded in the neural circuit of aggression independent of the housing conditions such as the orbitofrontal and medial prefrontal cortex, several nuclei of the amygdala, BNST, several hypothalamic regions, the LS, the VTA, the PAG, and

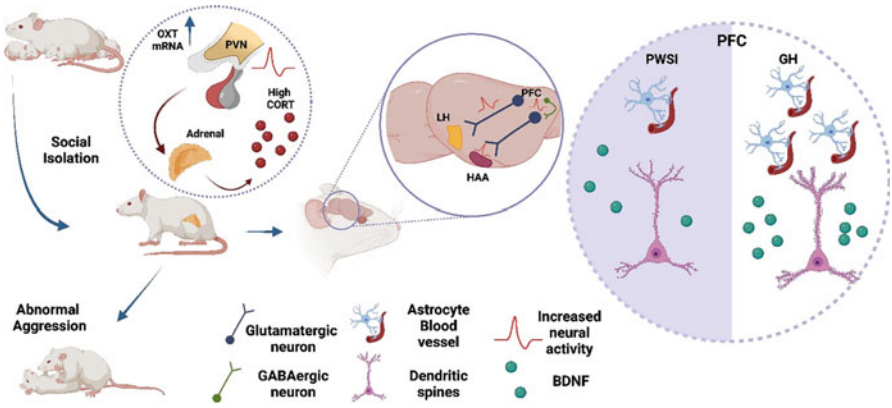

Fig. 1 Postweaning social isolation (PWSI) induces abnormal aggression and brain plasticity in Wistar rats. Total 8 weeks of social isolation after weaning strongly increases aggression in male Wistar rats. Isolated rats were found to present increased corticosterone (CORT) and elevated activation of the paraventricular nucleus of the hypothalamus (PVN) in response to an aggressive encounter as well as higher expression of oxytocin (OXT) mRNA in the same region. Additionally, plasticity changes were found in the prefrontal cortex (PFC) of isolated rats characterized by reduced number of astrocytes, blood vessels, dendritic spines, and levels of the brain-derived neurotrophic factor (BDNF). Functionally, GABAergic and glutamatergic neurons in the PFC were found to be hyperactivated after aggression, and PFC-lateral hypothalamus (LH) projections were found to modulate violent bites, whereas PFC-hypothalamic attack area (HAA, mediobasal hypothalamus) was found to regulate normal bites. Drawn using https://biorender.com.

the NAcc. Interestingly, some regions were hyperactivated specifically in PWSI males such as the PVN, mediobasal hypothalamus (hypothalamic-attack-area, HAA), the MeA, the basolateral amygdala (BLA), the cingulate, and the orbitofrontal cortex (OF) (Toth et al. 2012). The increased activation of the PVN is in line with previous evidence of an enhanced corticosterone response to aggression in PWSI males (Toth et al. 2011); interestingly, those animals also presented increased OXT mRNA (Oliveira et al. 2019). As OXT is known to reduce aggression in males (Calcagnoli et al. 2013, 2015; de Jong and Neumann 2017), it would be interesting to determine which neuronal population in the PVN is recruited by fighting in PWSI males.

Additionally, the combined evidence of increased activation of the anterior BNST (Toth et al. 2012) in PWSI males associated with increased V1aR binding in this region (Oliveira et al. 2019) might indicate an impaired AVP signaling leading to aggression. In fact, AVP release in the BNST was found to negatively correlate with aggression in male Wistar rats. Furthermore, the administration of synthetic AVP in the BNST reduced aggression in highly aggressive male rats (Veenema et al. 2010). It remains to be addressed whether similar mechanisms regulate aggression in PWSI males and females.

Recent studies have further dissected the neuroplastic mechanisms underlying abnormal aggression in PWSI males. Briefly, PWSI male rats exhibit a shrank prefrontal cortex (PFC, infralimbic IL, and prelimbic Prl); this was accompanied

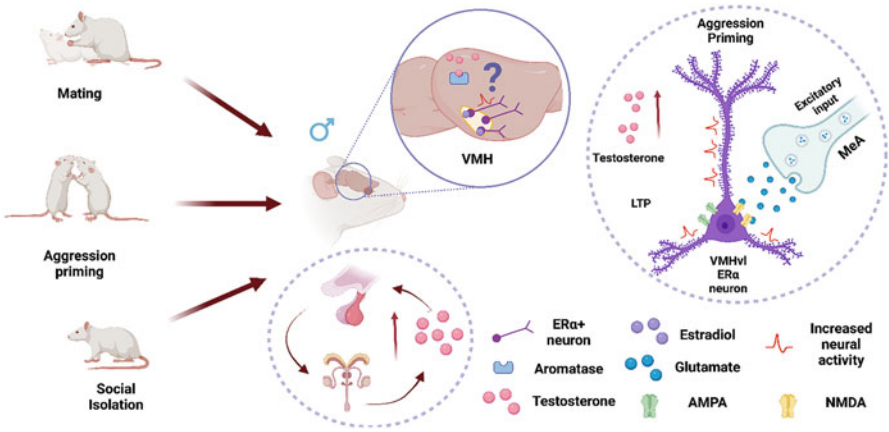

Fig. 2 Social experience enhances male aggression via testosterone. Mating, aggression priming, and social isolation exacerbated aggression as well as plasma testosterone in male rodents. In the brain activity of estrogen, receptor alpha (ERα) neurons in the ventrolateral part of the ventromedial nucleus of the hypothalamus (VMHvl) were found to be crucial for this enhanced aggression. Particularly, aggression priming was found to increase long-term potentiation (LTP) from the medial amygdala (MeA) projections to VMHvl-ERα neurons. Those neurons also presented increased dendritic spine density. Also, plasticity and behavioral alterations were found to be testosterone dependent. Yet, it remains to be addressed how testosterone acts on ERα neurons (probably via newly synthesized estrogens?) and whether aggression itself acts on the brain hubs regulating testosterone release or systemically at the level of the testis. Drawn using https://biorender.com.

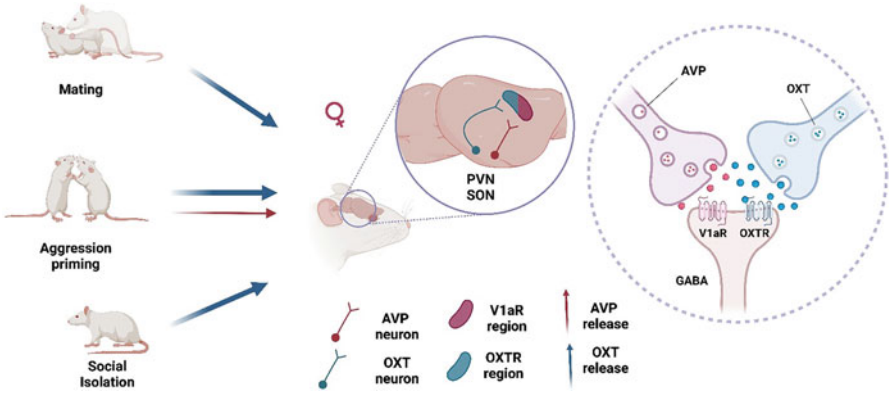

Fig. 3 Social experience enhances female aggression via oxytocin (OXT). Mating, aggression priming, and social isolation exacerbated aggression as well as brain OXT release in female Wistar rats. Particularly, socially isolated and aggression-trained female Wistar rats exhibited increased OXT and decreased vasopressin (AVP) release in lateral septum (LS) GABAergic neurons. It still remains to be addressed how OXT modulated the activity of the brain networks involved in aggression to generate escalated behavior. Also, the specific participation of OXT receptors (OXTR) and vasopressin 1a receptors (V1aR) coexpressed in GABAergic neurons in most of the limbic regions regulating fighting remains unknown. Drawn using https://biorender.com.

by reduced astrocyte density, vascularization, and dendritic spine density in this region. Surprisingly, neuronal activity was enhanced in PWSI in glutamatergic and GABAergic neuronal populations within the PFC (Biro et al. 2016). Particularly, glutamatergic populations were found to impinge in LH to induce violent bites (toward vulnerable targets) whereas projections to the HAA were found to induce normal bites (Biro et al. 2018) (Fig. 1).

Finally, recent finds have evidenced that the brain-derived neurotrophic factor (BDNF) might be involved in those plasticity-related mechanisms. BDFN mRNA was found to be reduced in the IL and MeA of socially deprived male rats compared to group-housed controls. Additionally, the number of neurons projecting from the ventral hippocampus to the PFC was reduced in PWSI rats; this was accompanied by an increase in the number of parvalbumin neuronal nets, which indicates a reopening in the plasticity window in the brain. Interestingly, resocialization associated with fluoxetine treatment for 3 weeks was found to normalize BDNF levels in both regions and reduce violent attacks (toward vulnerable targets) as well as to rescue ventral hippocampus changes. Those effects of fluoxetine and resocialization on aggressive behavior were linked to TrkB (BDNF receptor) activity as TrkB antagonism suppressed the effects of both treatments on violent aggressive behavior. Additionally, activation of TrkB alone decreased attacks toward vulnerable targets in those animals (Mikics et al. 2017) (Fig. 1).

Taken together, those results show that social isolation during early life generates abnormal aggression in both sexes, and disrupts the OXT and AVP systems. Particularly, in males, pathological aggression was found to be underlined by hyperarousal phenotype and plastic changes in the PFC which were BDNF-dependent (Fig. 1).

Adulthood Neurobiological Mechanisms

As mentioned before, social isolation is known to enhance aggression in adult male rodents (Borland et al. 2019; Elliott Albers et al. 2006; Ross et al. 2019; Toth et al. 2011; T. Yang et al. 2017; Zelikowsky et al. 2018); this was also reported to a less extent in females (Borland et al. 2019; Hashikawa et al. 2017; Oliveira and Bakker 2022; Oliveira et al. 2021; Ross et al. 2019).

In comparison with early life social isolation, not much is known about the neuronal mechanisms underlying increased aggression after adulthood social isolation. This might arise from several factors such as biological sex, duration of the social isolation period, and species differences. This section focuses on the already described neuronal mechanisms.

Total 9 days of social isolation reportedly increased the percentage of time spent on total aggressive behavior, keep down, threats, and attacks in female Wistar rats. Interestingly, isolated females in the receptive phases of the estrous cycle (proestrus or estrus, characterized by high levels of estradiol and progesterone (Yin and Lin 2023)) failed to show exaggerated aggression compared to group-housed controls. Those receptive females exhibited also lower levels of aggression compared to nonreceptive (metestrus or diestrus) isolated rats (V. E. M. Oliveira et al. 2021).

Those results suggest that sex hormones might buffer the effects of social isolation on aggression. Accordingly, social isolation for 4 or 24 days failed to affect Erα expression (Ruscio et al. 2018) in the neuronal network of aggression in highly aggressive female California mice (Silva et al. 2010).

Although appealing, those findings should be interpreted carefully as stimulation of VMHvl-ERα neurons was found to trigger attacks in virgin and lactating female CD1 mice. Additionally, single-housed female CD1 mice reportedly showed increased activity (c-FOS and in vivo calcium signals) in the VMHvl-Erα neurons after a confrontation with a juvenile (Hashikawa et al. 2017). Thus, altogether, this data indicates an intricate interplay among sex hormones, social isolation, and aggression in females, thereby more experiments are needed to properly investigate the underlying mechanisms. For a detailed review of the role of sex hormones in female aggression, please see (Oliveira and Bakker 2022).

In male mice, a clearer picture has been described regarding sex hormones, social deprivation, and aggressive behavior. Similarly to "aggression priming," social isolation itself was found to increase plasma testosterone in mice (Sayegh et al. n.d.); additionally, socially isolated California mice exhibited a higher number of ERα cells in the VMHvl (Ruscio et al. 2018). Results from the Shah group further dissected the interaction between VMHvl-ERα neurons (rather a progesterone receptor (PR), positive neurons coexpressed in the VMH in a ratio of 1:1 to ERα) and aggression. They have elegantly shown using refined behavioral protocols associated with gain and loss of function experiments that VMHvl-Erα-PR neurons drive aggression in isolated residents independently of chemosensing, gonadal hormones, or the aggression levels of the intruder. On the other hand, the same neurons were unable to drive aggression in socially housed mice except when olfactory chemodetection was suppressed (T. Yang et al. 2017).

Regarding the neuropeptide OXT, highly aggressive isolated female Wistar rats showed increased OXT content in their CSF after an aggressive encounter with a same-sex conspecific. Furthermore, aggression levels in those females positively correlated with OXT content in the CSF, indicating high OXT levels in the brain lead to heightened aggressive behavior in females. In line with that, increasing OXT release and content in the brain of low-aggressive group-housed females using chemo-, optogenetic, or pharmacological approaches enhanced female aggression (Oliveira et al. 2021). In hamsters, social isolation also increased aggressive behavior in both sexes. Interestingly no effect of isolation was found in OXTR binding in both sexes (Ross et al. 2019) which was consistent with the abovementioned study using female Wistar rats (Oliveira et al. 2021).

Regarding AVP, no effect of social isolation was seen in AVP content in the CSF of female Wistar rats (Oliveira et al. 2021). Nevertheless, V1aR receptor binding was particularly affected in highly aggressive male hamsters, with increased binding described in the PVN, AH, and LH whereas decreased binding was reported in the CeA, dorsal raphe, and BNST (Elliott Albers et al. 2006; Ross et al. 2019). In female hamsters, social deprivation only reduced V1aR binding in the BNST (Ross et al. 2019).

Other neuromodulatory systems such as the tachykinin 2/neurokinin B (Tac2/NKB) and nitric oxide (NO) systems have been also described to be affected by social isolation. Total 2 weeks of social isolation was found to increase aggression in male mice; this was accompanied by an overall upregulation of Tac2 expression in the CeA, dorso anterior BNST, and dorsomedial hypothalamus (DMH). Blockade of neurokinin 3 receptors (NK3R) acute- (before the RIT), chronically (during SI), or locally in the DMH (before RIT) decreased aggression in isolated animals. Finally either silencing $Tac2^{+}$ cells or knocking down Tac2 mRNA in the DMH strongly reduced aggression in these highly aggressive isolated male mice (Zelikowsky et al. 2018).

Total 2 weeks of social isolation was found to stimulate NO synthesis in the cortex of male mice; this was followed by high levels of aggression. Furthermore, inhibition of NO synthesis using ZL006, an NMDA-R-dependent NO synthesis inhibitor targeting specifically neuronal nitric oxide synthase (nNOS)/PSD95, reduced aggressive behavior in isolated mice (Yang et al. 2022b). Conversely, isolated nNOS-KO mice were found to display a higher number of attacks, boxing, and decreased attack latency compared to isolated wild types. Accordingly, NO synthesis inhibition systemically mimicked the effects of the deletion nNOS only in single-housed but not pair-housed mice (Trainor et al. 2007). Those results evidence a different role for synaptic (plasticity induced) and global NO on aggression; future studies should access the role of different nNOS neuronal populations on aggression. Additionally, the role of NO and Tac2 on aggressive behavior in females remains unclear.

Finally, the LS has emerged as an important inhibitory hub suppressing aggressive behavior in both sexes (Menon et al. 2021). Notably, a recent study in hamsters has evidenced sex and social experience-dependent effects on LS control of aggressive behavior (Borland et al. 2019). In detail, inhibition of the dLS via administration of muscimol (GABA-A agonist) was found to increase aggression in female hamsters independently of the housing condition. In contrast, dLS inhibition increased aggression only in isolated male hamsters. Finally, social isolation for 4 weeks decreases the ratio of extrasynaptic δ and synaptic y2 GABAA receptors in the dLS of both sexes, this suggests that social isolation might enhance aggression by increasing tonic inhibition in the LS (Borland et al. 2019). Accordingly, the GABAAδ receptor agonist mimics the effect of muscimol in male hamsters (Borland et al. 2019). This is in line with previous findings showing decreased activity of GABAergic neurons in the dLS of highly aggressive IST females (Oliveira et al. 2021).

Concluding Remarks

In rodents, aggressive behavior is instigated by different social environments and/or conditions. In an ethologically relevant context, once animals copulate they start displaying aggression to protect their potential mates from competitors (Aubry et al.

2022a; Koolhaas et al. 1980; Oliveira and Bakker 2022); this enables subjects to get access to the best mates available and, consequently, achieve reproductive success (Rosenthal and Ryan 2022).

Apart from reproductive-relevant settings, escalated aggression is also induced by engaging and winning successive fights, the so-called "winner effect," "aggression training," or "aggression priming"; this phenomenon shows that even the most hard-wired innate behaviors might become flexible once they are stimulated by experience (Wei et al. 2021).

The behavioral, ecological, and evolutive reasons behind aggression priming are not completely understood; this increased performance might emerge from the fact that aggressive experiences are rewarding for animals (Beiderbeck et al. 2012; Dai et al. 2022); thus, aggressive animals develop a type of addictive behavior seeking for new wins (Falkner et al. 2016; Golden et al. 2017). This increased reward might be the reason behind the neuroplasticity alterations reported here in the NAcc (Been et al. 2016; Staffend and Meisel 2012) and VMHvl (Stagkourakis et al. 2020) of trained rodents.

On a different side of the spectrum, the lack of social interactions and disruption of social homeostasis also originates a pathological form of aggression. Particularly early-life social deprivation generates abnormal aggressive behavior characterized by increased attacks, attacking juveniles, females in estrous, and anesthetized intruders as well as attacks toward vulnerable targets (belly, throat, head, and paws) (Haller 2013; Sandi and Haller 2015). Perhaps, this lack of social interactions directly affects animal social motivation to produce antisocial tendencies.

Regarding the biological factors promoting this facilitation of aggression, some systems seem to be shared by all three conditions. In male rodents, alterations in the social environment tend to lead to elevated levels of testosterone which might act in the VMHvl-ERα neurons to enhance aggression (Fig. 2). In females, on the other hand, the elevated release of the neuropeptide oxytocin seems to be the link between mating, aggression training, social isolation, and exacerbated aggression (Fig. 3). Future studies should dissect those systems and unravel the specific mechanisms leading to plasticity. Additionally, future studies should focus on the behavioral and evolutionary mechanisms by which aggression training and social isolation reinforce pathological aggression.

Applications of the Material

This chapter reviews how social experiences might affect neurobiology to trigger exaggerated aggression in preclinical rodent models. The results summarized here might help neuroscientists choose appropriate animal models to conduct their studies depending on whether they want to focus on evolutionary and ethologically relevant models or pathological aggression. Additionally, the data described here might help clinical neuroscientists to identify biomarkers of pathological aggression in a sex-dependent manner.

Key Facts:

Social experiences affect aggressive behavior in animals and humans. In male rodents, social experience enhanced aggression seems to be associated with high levels of testosterone. In female rodents, social experience enhanced aggression seems to be associated with high oxytocin release. Social deprivation during early life leads to plastic changes in the prefrontal cortex and abnormal aggression in rats. Social deprivation in adulthood affects several neurobiological systems such as oxytocin, vasopressin, nitric oxide, neurokinin B, and sex steroids.

Mini-Dictionary of Terms:

Resident intruder test (RIT): The resident intruder test is the paradigm used to test aggressive behavior in rodents. Briefly, in the test experimental animals (residents) are allowed to freely interact with a smaller (10–20% of the resident's body weight) and weaker con-specific (intruder).

Aggression-seeking: Aggression-seeking is characterized by voluntary (proactive) behavior in pursuing aggressive interactions.

Aggression-conditioned place preference (CPP): CPP is a test to evaluate aggression reward. Briefly, the test animals are habituated to a three-chamber arena and allowed to attack a con-specific in one of the compartments. On test day, animals will be allowed to freely explore the three chambers without receiving an intruder. In general aggressive animals (winners/residents) will spend more time in the context previously associated with the possibility to attack an intruder.

Aggression operant self-administration test: This test has been used in different settings, typically animals have to actively perform a task (lever pressing or nose poking) to get access to a smaller intruder that they can attack. Thus, this test measures proactive aggression or aggression-seeking as the animals voluntarily pursue opportunities to engage in aggressive interactions.

Proactive aggression: In humans, proactive or instrumental aggression has been characterized to be more goal-oriented and involves a certain level of preparation or planning. For example, a murderer preparing to attack their next victim. This type of aggression has been associated with low-arousal status and low cortisol levels and aggression disorders such as conduct and antisocial personality disorder.

Reactive aggression: Reactive or impulsive aggression is the type of aggression related to a reaction to stimuli, normally associated with anger or impulsivity. For example, punching someone after a heated discussion. This type of aggression is normally associated with high arousal and cortisol in humans and posttraumatic stress disorder.

Abnormal aggression: Abnormal aggression is the name given to pathological aggression expressed by rodents. Typically, characterized by i) a mismatch between provocation and response (high number of attacks or attacking in neutral arenas); ii)

disregard for species-specific rules such as attacking without signaling, attacking receptive females and juveniles, or attacking vulnerable targets (paws, head, throat, belly, and gonads); and iii) insensitivity toward the social signs of intruders characterized by attacking defenseless intruders (either submissive or anesthetized).

Sex hormones: Steroid hormones derived from cholesterol and produced by the gonads (testis or ovary). The most relevant types of sex steroids influencing aggressive behavior are estrogens (estradiol), progestogens (progesterone), and androgens (testosterone).

Oxytocin (OXT): Nonapeptide produced in the periventricular (PVN) and supraoptic nucleus (SON) of the hypothalamus involved in uterine contractions during labor and milk-ejection reflex. In the brain, oxytocin has been linked with social motivation, mating, maternal behavior, and aggression.

Vasopressin (AVP): The sister peptide of oxytocin expressed in the PVN, SON, medial amygdala, bed nucleus of stria terminalis, and olfactory bulb. Similarly to OXT, AVP has been characterized to influence multiple social behaviors in rodents ranging from social memory and maternal behavior to aggression.

Hypothalamic-attack-area (HAA): This is a conserved brain region found in almost all vertebrate taxa in the mediobasal hypothalamus. In mice, this region virtually corresponds to the ventromedial nucleus of the hypothalamus (VMHvl).

Summary Points

- Rodent models have been extensively used to study the neural underpinnings of aggression.
- The role of some external factors such as social experiences, or internal factors such as biological sex, have only recently gained attention.
- The composition of the social environment and/or the lack of social contact (social isolation) in different stages of development impact the display of aggressive behavior in rodents.
- Biological sex also interacts with changes in the composition of the social environment to affect the neuronal networks of aggression.

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