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The lateral septum in the regulation of aggression and social anxiety: Brain circuitry and neuroendocrine control [1)]

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The lateral septum (LS) is a subcortical brain region that relays neuronal signals from the hippocampus to multiple downstream structures such as the hypothalamus. Among various social behaviors, it is known that the LS plays a critical role in the regulation of aggressive behavior. Neurohistochemical studies revealed that neurons in the LS express neuropeptides such as oxytocin and vasopressin and their receptors as well as gonadal steroid hormone receptors such as androgen and estrogen. Progress in research tools for behavioral neuroscience studies advanced our knowledge on the role played by the LS in the neural network for the regulation of aggressive behavior and involvement of various neuroendocrine factors. Furthermore, it is now known that the LS is also controlling the levels of social anxiety which is closely related to the expression of aggressive behavior. In this article, we review recent findings on neuroendocrine regulation in the LS, as part of brain circuitries for aggressive behavior and social anxiety, with emphasis on animal research primarily mice and rats.

Key words: oxytocin, vasopressin, estrogen receptors, testosterone, hypothalamic and limbic brain regions

Introduction

The lateral septum (LS) is a subcortical brain region in the anterior part of the forebrain, located between the lateral ventricles and the middle of the brain (Risold & Swanson, 1997). LS relays neuronal signals from the hippocampus to multiple downstream structures such as the hypothalamus and midbrain (Anthony et al., 2014; Leroy et al., 2018; Risold & Swanson, 1997). The LS expresses not only neurotransmitters such as GABA and dopamine (Shin et al., 2018) but also many neuroendocrine factors. In particular, neuropeptides such as oxytocin and vasopressin, and gonadal steroid hormone-related proteins such as androgen and estrogen receptors are highly distributed in the LS (Borie et al., 2021; Cara et al., 2021; Horiai et al., 2020; Mitra et al., 2003; Oliveira et al., 2021; Sagoshi et al., 2020). Through neuroendocrine regulation on multiple neural networks, LS orchestrates social and non-social information and regulates several types of behavior. Specifically, a variety of social behaviors including aggressive (Leroy et al., 2018; Wong et al., 2016), sexual (Kondo et al., 1990), and maternal behavior (Curley et al., 2012), as well as, social anxiety (Shin et al.,

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2018) and social memory (Horiai et al., 2020) are known to be regulated by the LS. Among them, involvement of LS in the control of aggressive behavior has been studied for more than several decades (Compaan et al., 1993; Potegal et al., 1981; Wong et al., 2016). A dramatic increase in aggressive behavior caused by lesion of the LS is known as "septal rage", suggesting inhibitory control over aggressive behavior by the LS (Potegal et al., 1981; Wong et al., 2016). Moreover, recently, the role of the LS in social anxiety has received much attention (Shin et al., 2018). In this review, we discuss the role of the LS in neural circuits for these two types of social behaviors, i.e., aggressive behavior and social anxiety, and neuroendocrine regulation with emphasis on animal (including rats and mice) research.

Brief overview of neural circuits involved in aggressive behavior

Aggressive behavior is defined as overt behavior with intent on inflicting physical harm on another individual (Haller et al., 2006; Ogawa et al., 1997). Since outcomes of aggressive behavior, such as acquisition of mating partners and food resources, are generally advantageous for animals' survival, aggressive behavior has been conserved among a broad range of species. Laboratory rats and mice are often used in experimental animal models to study brain mechanisms of aggressive behavior. Two types of naturally occurring aggressive behavior, i.e., intermale aggression (eg., Lin et al., 2011; Stagkourakis et al., 2018) and maternal aggression (eg., Georgescu et al., 2022; Hasen & Gammie, 2005; for review, see Bosch & Neumann, 2012), are extensively studied in these species. Intermale aggression is expressed among male conspecifics for resources such as food, mating partners, and territory (Haller et al., 2006; Ogawa et al., 1997; Potegal et al., 1981; Trainor et al., 2006). In females, on the other hand, vigorous aggressive behavior is expressed during pregnant and postpartum periods to protect their offspring (Hasen & Gammie, 2005; Motta et al., 2013; Ogawa & Makino, 1984; Rosenblatt et al., 1996). Recently, an increasing number of studies on aggressive behavior exhibited by cycling females has also been reported (De Jong et al., 2014; Hashikawa et al., 2017; Oliveira et al., 2021). To assess aggressive behavior, a resident-intruder paradigm is often used (for review, see Nelson & Trainor, 2007). In this paradigm, a stimulus animal (intruder) is introduced into a cage of singly-housed experimental animal (resident). Since the latter recognizes his/her living cage as their own territory, vigorous aggressive behavior toward an intruder can be observed. To avoid confounds of counter attacks by intruders to residents, either juvenile or olfactory bulbectomized males or females (especially for tests of female experimental animal) are often used as intruders.

The brain circuits that control aggressive behavior consist mainly of the hypothalamus and limbic brain regions. Effects of local brain lesions on the levels of aggressive behavior have been combined with examination of immediate early genes (IEG's; as markers of neuronal activity, induced by aggression) and are widely used to determine brain region(s) involved in aggressive behavior. These studies have identified the following brain sites that comprise the brain circuit of aggression in mice and rats: 1) the orbitofrontal cortex (OFC); 2) lateral septum (LS); 3) bed nucleus of the stria terminalis (BNST); 4) medial preoptic area (MPOA); 5) paraventricular nucleus (PVN); 6) ventromedial part of the hypothalamus (VMH); 7) medial amygdala (MeA); 8) ventral premammillary nucleus (PMv); 8) periaqueductal grey (PAG); and 9) dorsal raphe nucleus (DRN) (Bayless et al., 2019; Lin et al., 2011; Nakata et al., 2016; Stagkourakis et al., 2018; Takahashi et al., 2010; Tan et al., 2021; Unger et al., 2015; Wong et al., 2016; Xu et al., 2019; Zhu et al., 2021). In male mice and rats, it has been reported that lesions of the BNST and MeA inhibit intermale aggressive behavior, whereas lesions of the OFC and LS increase intermale aggressive behavior (De Bruin et al., 1983; Wong et al., 2016; for review, see Nelson & Trainor, 2007). Investigation of the expression of the IEG, c-Fos, revealed several brain regions activated by aggressive behavior including the LS, BNST, PVN, and MeA (Haller et al., 2006). In females, lesions of the MPOA and PMv decrease maternal aggression, while lesions of the LS and PVN increase maternal aggression (Flannelly et al., 1986; Giovenardi et al., 1998; Motta et al., 2013; Rosenblatt et al., 1996).

Recently, newly developed methods for brain site- as well as cell type - specific stimulation such as optogenetics and chemogenetics greatly help us to determine more precisely the connection between neural activity of targeted brain regions and expression of aggressive behavior. Optogenetic activation of the ventrolateral portion of the VMH (VMHvl) strongly induced aggressive behavior in both male and female mice, while inhibition of neuronal activity decreased aggressive behavior (Hashikawa et al., 2017; Lee et al., 2014; Lin et al., 2011). Surprisingly, optogenetic activation of VMHvl induced aggressive behavior not only toward male conspecifics but also toward female conspecifics and inanimate objects, which generally should not be attacked (Lin et al., 2011). These findings indicate that the VMHvl is one of the brain regions that control expression of aggressive behavior and experimental (or artificial) activation evokes aggression. Besides VMHvl, a number of other brain regions has also been examined as potential brain sites responsible for aggression. Consistent with lesion studies, chemogenetic inhibition of aromatase-expressing neurons in the BNST and MeA decreased aggressive behavior in male mice (Bayless et al. 2019; Unger et al., 2015). Moreover, optogenetic activation of dopamine transporter-expressing neurons in the PMv induced aggressive behavior in male mice (Stagkourakis et al., 2018). Although these brain regions have been suggested as aggression-facilitating, brain regions that inhibit aggressive behavior have also been identified. Similar to lesion studies, the medial prefrontal cortex (mPFC) and LS have been reported to be involved in inhibitory regulation of aggressive behavior. Both chemogenetic activation of the mPFC and optogenetic activation of the LS inhibited aggressive behavior in male mice (Leroy et al., 2018; Tan et al., 2021; Wong et al., 2016).

Role of the LS in the expression of aggressive behavior

The LS is considered as an inhibitory locus for aggressive behavior, since lesion studies conducted in the early 1900s consistently showed elevation of aggressive behavior (Spiegel et al., 1940). When the septal area located anterior to the hypothalamus was removed, extremely strong rage responses called "septal rage" were observed in cats (Spiegel et al., 1940). In contrast, electrical stimulation of septal regions reduced aggressiveness in cats (Siegel & Skog, 1970). Also in rodents, lesion or pharmacological inactivation of the LS increased aggressive behavior (Lee & Gammie, 2009; McDonald et al., 2012; Potegal et al., 1981; Wong et al., 2016; for review, see Albert & Chew, 1980). Since it has been shown that more than 80% of the LS neurons are GABAergic, these inhibitory neurons may be responsible for suppression of aggressive behavior (Wong et al., 2016; Zhao et al., 2013). In fact, optogenetic activation of LS GABAergic neurons terminated ongoing aggressive behavior in male mice (Wong et al., 2016).

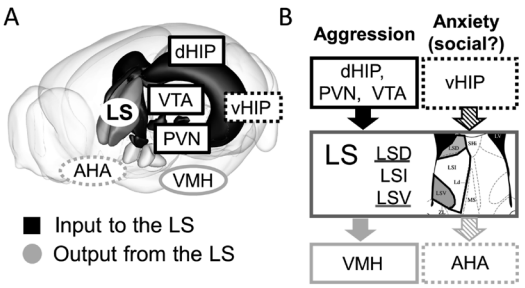
On the other hand, studies that mapped neuronal activation induced by expression of aggressive behavior with the use of c-Fos, provided inconsistent results. Haller et al. (2006) have used mouse lines selectively bred for aggressiveness based on attack latency, i.e., aggressive (short attack latency: SAL) and non-aggressive (long attack latency: LAL). They compared c-Fos expression induced by aggressive encounter between males in several brain regions including the LS. They found that the number of c-Fos positive cells was higher in LAL mice compared to SAL mice, so that the LS was more activated in non-aggressive animals (Haller et al., 2006). Similarly, in research using Wistar rat lines selectively bred for anxiety levels (measured in the elevated plus maze), i.e., low anxiety-related behavior line (LAB) and high anxiety-related behavior line (HAB), the HAB line showed lower levels of aggressive behavior and higher levels of c-Fos expression in the LS compared to the LAB line (Beiderbeck et al., 2007). Since increased neuronal activity in the LS was seen in individuals with lower levels of aggressive behavior, these studies support the idea of inhibitory modulation of aggressive behavior by the LS. In contrast, intense aggressive behavior induced by social isolation during post-weaning period was correlated with higher number of c-Fos neurons in the LS in Wister rats (Toth et al., 2012). Furthermore, the number of immunopositive cells for the IEG's pERK and pCREB, in the ventral LS (LSV) was positively correlated with the levels of

aggressive behavior in California mice (Trainor et al., 2010). These results suggest facilitatory effect of the LS in the regulation of aggressive behavior. Inconsistent results may be due to the fact that each study analyzed different sub-regions of the LS. The LS is broadly spread from anterior to middle part of the forebrain and consists of 3 main subregions: 1) dorsal LS (LSD); 2) intermediate LS (LSI); and 3) LSV (Paxinos & Franklin, 2019). Haller et al. (2006) analyzed a section from the middle part (bregma 0.62mm) of the LSI, whereas Trainor et al. (2010) focused on a section in the posterior part (bregma 0.26mm) of the LSV. Toth et al. (2012) used 3 sections from middle part of the LS (bregma 0.70 to 0.20mm), and Beiderbeck et al. (2007) used 2 sections from the septal brain area (detailed coordinates were not reported). The last two studies probably analyzed the entire LS including LSD, LSI, and LSV. These subregions of the LS may be differently involved in aggressive behavior. In fact, it is reported that activation patterns of LSD and LSV respond exactly opposite during aggressive behavior in electrophysiological recording studies (Leroy et al., 2018; Oliveila et al., 2021). All these findings collectively suggest the importance to investigate possible sub region-specific roles of the LS in the regulation of aggressive behavior.

LS plays a critical role in the neural circuit of aggressive behavior

Tracing studies for neuronal projections of the LS have identified medial hypothalamic area as one of main downstream regions of the LS (Risold & Swanson, 1997). The medial hypothalamic area includes aggression-related brain regions such as the MPOA and the VMH (Lin et al., 2011; Nakata et al., 2016). Among them, output to the VMH from the LS plays a critical role in modulating aggressive behavior (Figure 1-A). Recent studies with the use of optogenetics have revealed that aggressive behavior is suppressed by the LS-VMH neural circuit, which is modulated by an input from the hippocampus to the LS (Leroy et al. 2018). Projections from the CA2 field of the hippocampus activate LSD neurons via pre-synaptically acting vasopressin. The LSD then inhibits VMH-projecting

Figure 1. Major neural inputs and outputs related to aggressive behavior and anxiety in the LS.



Note. A,B, The LS receives aggression-related projections from the dorsal hippocampus (dHIP), ventral hippocampus (vHIP), ventral tegmental area (VTA), and paraventricular nucleus (PVN). The LS sends neural projections to the ventromedial part of the hypothalamus (VMH), and anterior hypothalamus (AHA). The image of the brain was made by using SBA composer (Bakker et al., 2015). The LS-VMH projection may be involved in aggressive behavior while the LS-AHA projection may be involved in anxiety. ■: inputs to the LS. ●: outputs from the LS.

neurons in the LSV which are inhibitory for aggression. Therefore, chemogenetic inhibition of the CA2-LSD pathway results in suppression of aggressive behavior (Leroy et al., 2018).

The LS may also be involved in stress-induced suppression of aggressive behavior. The PVN provides monosynaptic glutamatergic projections to the LSV, and activation of this pathway increases stress responses and suppresses aggressive behavior (Xu et al., 2019, Figure 1-A). In addition, dopaminergic input from the ventral tegmental area to the LS is known to promote aggressive behavior (Mahadevia et al., 2021, Figure 1-A).

Involvement of oxytocin and vasopressin in aggressive behavior.

Oxytocin (OT) and vasopressin (AVP) are peptide hormones known to regulate several physiological phenomena peripherally, such as parturition, lactation, and blood pressure (for review, see Donaldson & Young, 2008; Rigney et al., 2022). OT and AVP can act also as neuropeptides in the brain to regulate several social behaviors, including

aggressive behavior and social anxiety (Borie et al., 2021; Compaan et al., 1993; Oliveira et al., 2021). Synthesized mainly in the hypothalamic PVN and supraoptic nucleus (SON), OT and AVP act on oxytocin receptors (OTR) and vasopressin receptors (AVPR: V1aR, V1bR, and V2R), respectively. Among them, OTR, V1aR and V1bR are widely expressed in brain regions controlling social behaviors including the VMH, MeA, and LS (Horiai et al., 2020; Nasanbuyan et al., 2018; Yoshida et al., 2009). Magnocellular neurons of the PVN send fibers to these brain regions (Liao et al., 2020; Rood et al., 2013). (It should be noted that V2R is highly distributed in the kidney, not in the brain (Hirasawa et al., 1994). Thus, neuroendocrine modulation of AVP may act mainly through V1aR and V1bR in the brain.) Also, it is shown that there are dense projections of AVP immunopositive cells in the BNST to the LS (Compaan et al., 1993; for review, see De Vries & Panzica, 2006).

Generally, OT has been thought to inhibit aggressive behavior in both sexes, since higher expression of aggressive behavior is often seen in animals with lower levels of OT. Male rats showing excessive aggressive behavior have lower levels of transcription of OT in the PVN than rats showing normal levels of aggressive behavior (Calcagnoli et al., 2014). Suppression of aggressive behavior in male mice caused by early life stress of maternal separation coincided with increased OT immunoreactivity in the PVN (Tsuda et al., 2011). Unlike males, in female mice, maternal separation stress elevated levels of maternal aggression while neuronal activity of OT positive cells in the PVN was decreased (Veenema et al., 2007). Moreover, highly aggressive female rats showed lower levels of activation of OT neurons in the PVN compared to non-aggressive rats (De Jong et al., 2014). Acute ICV injection of OT in male rats actually inhibited both inter-male (Calcagnoli et al., 2013) and inter-female aggression in rats (De Jong et al., 2014). These findings indicate that OT inhibits aggressive behavior in both sexes. On the other hand, studies using OT knockout (KO) mice provided contradictory results. Lazzari et al. (2013) reported that expression of aggressive behavior was suppressed in global OT KO male mice. Similarly, it was reported that average duration of aggressive encounter was decreased in OT KO male mice, suggesting a facilitative control by OT of aggressive behavior (DeVries et al., 1997).

AVP is known to facilitate aggressive behavior. In both males and lactating females of AVP KO rats, aggressive behavior toward a male opponent was decreased, compared to wildtype (WT) (Fodor et al., 2014). In the brain, AVP acts through two types of receptors, V1aR and V1bR, and both pathways seem to facilitate aggressive behavior. It has been shown that injection of AVP into the anterior hypothalamus (AHA) promotes aggressive behavior, while injection of V1aR antagonist in the AHA inhibits aggressive behavior in male hamsters (Caldwell & Albers, 2004; Ferris & Potegal, 1988). These facilitatory regulations by AVP via V1aR were also observed in male voles. It was revealed that formation of pair-bonding increased aggressive behavior, which was suppressed by blockade of V1aR in the AHA (Gobrogge et al., 2009). These findings provide evidence for facilitatory control of aggressive behavior via V1aR. However, it has been reported that expression of aggressive behavior was not disrupted in V1aR KO in male mice (Wersinger et al., 2007), but rather inhibited in V1bR KO male mice (Wersinger et al., 2004). Since oral administration of V1bR selective antagonist blocked aggressive behavior in male hamsters (Blanchard et al., 2005), both V1aR and V1bR may be involved in the facilitatory action of AVP on aggression.

Oxytocin and vasopressin action in the LS for the regulation of aggressive behavior

It is known that OTRs and AVPRs (V1aR and V1bR) are localized in the LSD and LSV, and OT and AVP signaling via these receptors have been suggested to be involved in male aggressive behavior (Compaan et al., 1993; Lee et al., 2019). Regarding OT, however, previous studies have shown inconsistent results. Highly aggressive male rats had low OTR-binding in the LSV, whereas dominant male mice showed higher OTR-binding compared to subordinates in the whole LS (Lee et al., 2019; Lukas et al., 2010). Although pharmacological examination with micro infusion of OT and OT antagonist into targeted brain areas is the most suitable to detect the exact role of local

OT action (Calcagnoli et al., 2015; Harmon et al., 2002), this type of analysis has not been done in the LS for male aggressive behavior.

In contrast to OT, potential roles and mechanisms of action of AVP in the LS in the control of male aggressive behavior have been well studied with the use of a number of different analysis tools. These studies revealed that unlike facilitatory effects of AVP in the other brain sites reviewed above, AVP in the LS may not simply act as facilitatory for male aggression. For instance, as stated above, LS is innervated by AVP producing cells in the BNST but the density of AVP positive fibers in the LS negatively correlates with male aggression in mice and rats (Compaan et al., 1993; Everts et al., 1997). On the other hand, infusion of AVP and V1aR antagonist into the LS failed to induce any changes of aggressive behavior in male rats (Compaan et al., 1993). A recent study focusing on V1bR in the LS revealed a potential role of AVP in neural circuit involved in facilitation of male aggression (Leroy et al., 2018) using fiber-photometry recording and chemogenetic manipulation of neuronal activity, the authors examined the neural projection from the hippocampus CA2 to the LSD. They found that neurons in this pathway were specifically active while male mice were showing aggressive behavior such as biting. Chemogenetic inhibition of CA2-LSD projection successfully suppressed aggressive behavior. In addition, neurons in the CA2 and their terminals in the LSD expressed V1bR, and infusion of V1bR antagonist into the LSD inhibited aggressive behavior. These results suggest that AVP action through V1bR in the LSD serves as facilitatory in neural circuit that promotes male aggressive behavior.

In terms of female aggressive behavior, a recent study by Oliveira et al. (2021) reported a possible role of OT and AVP in the LS. They examined behavioral effects of local infusion of OT and OT antagonist into the LS and reported that OT signals in the LSV increased inter-female aggression in rats. OT infusion as well as activation of fibers of OT neurons in the LSV increased aggressive behavior in group-housed female rats. On the other hand, in isolated female rats, which express high levels of aggressive behavior, OT antagonist infusion in both ICV and LSV, inhibited aggressive behavior. These findings suggest that OT in the LSV is facilitatory for female aggressive behavior. The study by Oliveira et al. (2021) also examined the AVP system in the LS. Aggressive behavior was inhibited by AVP infusion to the LSD in isolated female rats and increased by AVP antagonist infusion in group-housed female rats. Furthermore, the same authors reported that highly aggressive isolated female rats showed reduced V1aR binding in the LSD. These findings suggest that AVP in the LSD acts as inhibitory in regulating female aggressive behavior. It should be noted that based on the study by Oliveira et al. (2021), OT and AVP may be involved in female aggressive behavior through different mechanisms, i.e., facilitation by OT in the LSV and inhibition by AVP in the LSD. Moreover, although it is not possible to compare directly, inhibitory action of AVP in the LSD on aggressive behavior in female rats is contrasted with facilitatory action on male mouse aggression (Leroy et al., 2018) as described above.

Involvement of testosterone and estradiol in aggressive behavior

Testosterone (T) is a gonadal steroid hormone and controls various male social behaviors including aggression (for review, see Cunningham et al., 2012). T is secreted into the blood stream from the testes and generally acts on androgen receptors (AR) in the whole body, including the brain. In the brain, T acts not only through AR but also through two types of estrogen receptors (ER), ERα and ERβ, after being converted to estradiol (E2) by aromatase. Therefore, ER-mediated neuroendocrinological action of gonadal steroid hormones occur in both males and females (for review, see Roselli et al., 2009). In general, signaling pathways of T and E2 are mediated by nuclear receptors. In case of T, it passes through the cell membrane and binds to AR located in the cytoplasm. After that, ligand-bound AR forms dimers and translocates to the nucleus. The dimers of AR then act on DNA sequences called androgen response element and modulates gene expression (for review, see Cornil et al., 2012; Smith & Walker, 2014). Similarly, dimers of ligand-bound ERs interact with estrogen response element on DNA and

regulates gene transcriptions. Through these genomic pathways, both T and E2 regulate male social behaviors by changing transcription of downstream genes coding for various molecules including neurotransmitters, peptide hormones, receptors, enzymes, etc., in a brain region-specific manner.

In males, castration has been used as experimental treatment to control circulating levels of T in several species of laboratory animals. Most previous studies reported that castration greatly reduced the levels of aggression suggesting a facilitatory role of endogenous T (for review, see Zuloaga et al., 2008). Since immunohistochemical studies revealed that AR, ERα and ERβ are highly expressed in many aggression-related brain areas (Cara et al., 2021; Merchenthaler et al., 2004; Mitra et al., 2003), possible roles played by each receptor and brain site(s) have been investigated extensively.

Androgen receptors

Among signaling pathways of T, AR-mediated regulation of aggressive behavior has been examined by several methods such as AR KO mice and systemic and brain-site specific application of antagonists in mice and rats. In AR-null mutant male mice (which do not express AR in the whole body), aggressive behavior was markedly reduced (Sato et al., 2004). Similarly, neuron specific AR KO male mice exhibited greatly reduced levels of aggressive behavior (Juntti et al., 2010; Marie-Luce et al., 2013; Raskin et al., 2009; Studer et al., 2015). Although studies in AR deficient male mice consistently showed a facilitatory role of AR in aggressive behavior, findings with AR blockers are largely controversial. Cyproterone acetate (CA) and flutamide (FLU) are widely used as AR blockers, which prevent androgen (both T and dihydrotestosterone) binding to the AR. Both CA and FLU failed to suppress intermale aggressive behavior in mice (Brain et al., 1974; Clark & Nowell, 1979, 1980; Heilman et al., 1976), although electrical shock-induced aggression was suppressed by CA in male rats (Prasad & Sheard, 1981). These differences between the results of AR KO and antagonist infusion may be due to possible T actions during the developmental period. It is known that steroid hormones are involved in developmental changes of sex specific brain structures through their receptors, so called organizational action. Organizational action is endocrine response that causes irreversible changes in the neural substrates and brain structures by steroid hormone surge during critical periods such as perinatal and pubertal (for review, see McCarthy & Arnold, 2011). Therefore, in male AR KO mice, in addition to lack of AR at the time of testing in adult, i.e., activational action of T, neural substrates for aggressive behavior may be disrupted, so that expression of aggressive behavior was suppressed. Also, lack of suppressive effects of AR antagonists may be partly due to the fact that ERα and ERβ are intact. Binding of aromatized T to these receptors may be sufficient to maintain aggressive behavior.

Estrogen receptors

Since not only T but also E2 replacement restored aggressive behavior in castrated male mice, aromatization of T to E2 plays a critical role in the induction of aggressive behavior (Finney & Erpino, 1976; Sato et al., 2004; Toda et al., 2001). A series of studies with the use of knockout mice for either ERα or ERβ have reported involvement of each receptor in the regulation of male aggressive behavior by aromatized T. Ogawa et al. (1997) used global ERα KO male mice and found that aggressive behavior was greatly reduced. Similar results were also reported in follow-up studies (Ogawa et al., 1998, 2000). These results suggest a facilitatory role of ERα in aggressive behavior. In contrast to ERα, effects of ERβ KO appeared more complicated. Aggressive behavior of ERβ KO male mice was higher than WT on day 1 in a three-days test, suggesting inhibitory regulation of aggressive behavior by ERβ (Ogawa et al., 1999, 2000). In a later study, experimental mice were divided into three age groups: 1) pubertal (5 weeks old); 2) young adult (12 weeks old); and 3) adult (19 weeks old) (Nomura et al., 2002). Consistent with earlier findings, aggressive behavior was increased in ERβ KO mice but only in pubertal and young adult groups, suggesting age dependent effects due to a lack of ERβ (Nomura et al., 2002). In a study examining the effects of estradiol benzoate (EB; a more stable form of E2) treatment in castrated male mice, ERβ KO mice showed significantly higher

levels of aggressive behavior than WT mice, especially at higher doses (Nomura et al., 2006). This may be caused by the combination of E2 facilitatory effects through ERα and inhibitory effects through ERβ on aggressive behavior. Unlike in WT mice in which both ERα and ERβ were intact, only facilitatory action via ERα, but not inhibitory action via ERβ, was working in ERβ KO mice. Therefore, aggressive behavior was over expressed by EB treatment in ERβ KO mice. Collectively, these findings in KO mice suggest that estrogenic action of T through ERα promotes aggressive behavior while ERβ inhibition modulates ERα-induced aggressive behavior (for review, see Handa et al., 2012; Ogawa et al., 2020).

Since both ERα and ERβ are widely expressed in aggression-related brain areas, brain site specific roles of ERα and ERβ have been examined by using adeno-associated virus (AAV)-mediated RNA interference (RNAi) methods. ERα knockdown (KD) studies in outbred male mice have revealed that the VMH and MeA are brain sites responsible for facilitation of aggressive behavior via ERα through organizational and/or activational action of gonad steroids (Sano et al., 2013, 2016). In the MPOA, on the other hand, both ERα and ERβ KD in adulthood did not affect aggressive behavior. However, ERβ KD, but not ERα KD, before onset of the pubertal period suppressed expression of aggressive behavior in adult male mice (Nakata et al., 2016). Therefore, in the MPOA, organizational action of T via ERβ may modulate neural substrates for aggressive behavior. Unlike ERα, however, brain areas responsible for inhibitory estrogenic action through ERβ are still not completely understood.

Possible role of androgen and estrogen receptors in the LS in the regulation of aggressive behavior

The LS is known to express AR, ERα, and ERβ (Cara et al., 2021; Mitra et al., 2003; Sagoshi et al., 2020). AR is highly localized in the LSD and LSV (Cara et al., 2021), and ERα is expressed mainly in the caudal part of the LSV (Hasunuma et al., 2021). Cellular localization of these two receptors appear to be partly overlapped in the LSV, since the number of AR was decreased in the LS in transgenic mouse in which AR was disrupted only in ERα expressing neurons (Sagoshi et al, 2019). Recently, the distribution patterns of ERβ in the LS were identified with the use of newly developed transgenic ERβRFP mice in which ERβ expressing cells were labelled with red fluorescent protein, RFP (Sagoshi et al., 2020). It was found that ERβ was highly expressed in the rostro-medial part of the LS and rostral part of the LSV (Hasunuma et al., 2021). This study also revealed that distribution of ERα and ERβ was distinctively different and the two types of ERs were rarely co-expressed in the same neuron (Hasunuma et al., 2021). This is contrasts with other brain regions including the BNST and MPOA in which ERα and ERβ are highly co-localized. Therefore, T action through ERα and ERβ in the LS may be significantly different from other brain areas (Sagoshi et al., 2020).

It has been suggested that AR, ERα, and ERβ in the LS may play a role in the regulation of aggressive behavior by gonadal steroids. Regarding AR, involvement in aggressive behavior was reported by Clinard et al. (2016). In this study, effects of repeated winning or losing experience in social encounters on plasma levels of T and number of AR-expressing cells in the LSV were examined in male hamsters. Dominant hamsters showed higher levels of aggressive behavior during 15 minutes encounter with an opponent who had elevated plasma T levels. They also had significantly higher number of AR expressing cells in the LSV, compared to subordinate hamsters after 14 days of winning experience. These results suggest that T action through AR in the LSV may be responsible for the facilitatory control of aggressive behavior (Clinard et al., 2016). To definitively understand the relationships between aggressive behavior and AR in the LS, more direct evidence with the use of site-specific AR KD and/or AR antagonist infusion is necessary.

Previous studies using ER gene KO mice have hypothesized that ERα and ERβ regulate male aggressive behavior in different directions: ERα promotes and ERβ inhibits aggressive behavior (Ogawa et al., 1997, 1999, 2000; Nomura et al., 2002, 2006). Although correlational, Trainor et al. (2006) and Trainor, Rowland, and Nelson (2007) reported a similar relationship between expression

ERα or ERβ and levels of aggressive behavior. In a seasonally breeding rodent species, *Peromyscus polionotus*, they studied effects of photoperiod on the expression of ERα and ERβ in the LSV. They found that mice expressed higher levels of aggression during a short day condition (8 hour light / 16 hour dark) than in a long day condition (16 hour light / 8 hour dark). The number of ERα expressing cells in the LSV was much higher in the short day condition than in the long day condition and positively correlated with aggressive behavior. In contrast, the number of ERβ expressing cells in the LSV was lower in the short day condition than in the long day condition (Trainor et al., 2007). Positive correlations between aggressive behavior and ERα expression in the LS was also observed in male CD-1 mice (Trainor et al., 2006). These results suggest that aggressive behavior may be facilitated by increased levels of ERα and suppressed by increased levels of ERβ in the LSV. Although brain site(s) responsible for inhibitory regulation of aggressive behavior through ERβ have not been determined definitively with local manipulation of expression and action of ERβ, the LS is certainly a potential candidate.

Brief overview of neural circuits of social anxiety

Social anxiety in humans is part of an anxiety disorder which is defined as anxiety toward social subjects (B Stein & D Stein, 2008). In the clinical field, criteria for the diagnosis of social anxiety have been established in the DSM-5 (Kupfer, 2016). In animal studies, Neumann et al. (2010) have defined anxiety as "an emotional anticipation of an aversive situation" which reflects stressful emotions toward threat in a species-specific manner (for review, see Neumann et al., 2010). Also, assessment of social anxiety in animal models has been established.

To assess social anxiety in rodents (particularly in rats and mice), social investigation tests and social interaction tests have been used (Douque-Wilckens et al., 2020; Tomihara et al., 2009; Tsuda & Ogawa, 2012; Tsuda et al., 2014). In these tests, a 'stimulus' animal is placed in a cylinder in the center or next to a wall of a test cage. It is generally hypothesized that if experimental animals' social anxiety is high, their investigation toward the cylinder and time spent around the cylinder would be suppressed. One advantage of these tests is that social anxiety can be assessed separately from social interest as displayed by sniffing toward the cylinder from a distance (e.g., "sniffing from corner") by stretching out the body (Tsuda & Ogawa, 2012). Sitting at the corner of the test cage suggests high anxiety, whereas sniffing toward stimulus animals is interpreted as social interest. Three-chamber test paradigm, which was originally developed to assess place preference and social discrimination, has also been used to assess social anxiety (Horiai et al., 2020; Shin et al., 2018). In this test, a subject animal is introduced into the central chamber and allowed free access to two side chambers, in which either a 'stimulus' animal containing cylinder or an empty cylinder is placed. Time spent in each chamber and amount of sniffing toward each cylinder are recorded as measures of social investigation. Higher values are interpreted as lower levels of social anxiety and higher levels of social interest (Shin et al., 2018).

Brain areas involved in the regulation of social anxiety include the mPFC, LS, BNST, PVN, basolateral amygdala (BLA), VTA, and ventral hippocampus (vHIP) (Clipperton-Allen et al., 2012; Douque-Wilckens et al., 2020; Felix-Ortiz & Tye, 2014; Felix-Ortiz et al., 2016; Gunaydin et al., 2014; Huang et al., 2021; Rigney et al., 2021a). It should be noted that these brain regions are also known to regulate anxiety-like behavior in non-social context (Anthony et al., 2014; Felix-Ortiz et al., 2013; Gunaydin et al., 2014; Jennings et al., 2013; Kim et al., 2013; Lamontagne et al., 2016; Yuan et al., 2019). A number of recent studies described a role played by the BLA in the control of social anxiety (Felix-Ortiz & Tye, 2014; Felix-Ortiz et al., 2016). Optogenetic activation of the BLA elicited a decrease of social investigation. Neural outputs from the BLA to the mPFC and vHIP are identified as part of a neural circuit which potentiates the levels of social anxiety (Felix-Ortiz et al., 2016; Felix-Ortiz and Tye, 2014). In addition, it has been demonstrated that input from the mPFC to the BLA may also be part of anxiogenic neuronal circuitry for social anxiety (Huang et al., 2020). This BLA-centered neural circuit also is responsible for an

anxiogenic control of anxiety-like behavior in non-social contexts (Felix-Ortiz et al., 2013, 2016; Felix-Ortiz and Tye, 2014; Kim et al., 2013; Tye et al., 2011). Therefore, social anxiety may be modulated in the BLA which may constitute part of the general neural network for anxiety.

Role of the LS in the neural circuitry for the regulation of social anxiety

It is known that the LS also plays a role in the control of anxiety-like behavior in both non-social and social context. As for its role in non-social anxiety, it is reported that chemical stimulation of the LS suppressed anxiety in rats (Yadin et al., 1993). Also, benzodiazepines and neuropeptide Y infusion into the LS produced anxiolytic effects in rats (Olivera-Lopez et al., 2008; Pesold & Treit, 1994). On the other hand, infusion of corticotropin-releasing factor receptor type 2 (Crfr2) agonist into the LS increased anxiety-like behavior in the elevated plus maze and light dark transition test in mice (Henry et al., 2006; Radulovic et al., 1999). In addition, optogenetic activation of Crfr2 expressing neurons in the LS increased anxiety levels, measured in the elevated plus maze, suggesting an anxiogenic role for LS Crfr2 expressing neuronal activity (Anthony et al., 2014).

It has been reported that the LS may be responsible for the reduction of social anxiety levels. Infusion of neuropeptide Y into the LS lowered social anxiety in male rats (Kask et al., 2001). Since more than 80 % of the LS neurons are GABAergic, it is likely that neuropeptide Y receptors are expressed in inhibitory neurons (Wong et al., 2016; Zhao et al., 2013). Therefore, infused neuropeptide Y may inhibit social anxiety by acting on inhibitory neurons. In addition, behavioral impairments such as elevated levels of social anxiety caused by early life stress were reversed by optogenetic activation of dopamine receptor 3 (Drd3) expressing neurons in the LS (Shin et al., 2018). This study also reported that Drd3 expressing neurons densely innervated the AHA. Therefore, it is hypothesized that the neural projection from the LS to the AHA may be part of the neural circuitry for social anxiety, although direct evidence is still missing.

On the other hand, the LS is well established as part of the neural circuit for anxiety-like behavior in non-social contexts. The LS is innervated by hippocampal regions, which are known to regulate anxiety-like behavior (Felix-Ortiz et al., 2013; Felix-Ortiz & Tye, 2014; Risold & Swanson, 1997). It was reported that chemogenetic activation of the vHIP-LS pathway elevated the levels of anxiety measured in the open field test and elevated plus maze (Parfitt et al., 2017). In the LS, Crfr2 expressing neurons send dense neural projections to the AHA, which may play a role in the modulation of anxiety (Anthony et al., 2014). Optogenetic activation of the LS-AHA projection actually increased anxiety-like behavior, and inhibition suppressed anxiety-like behavior (Anthony et al., 2014). Therefore, the LS may be involved in the regulation of anxiety-like behavior in general, by integrating the input from the vHIP and the output to the AHA. Whether the vHIP may also be involved in the control of social anxiety via LS-AHA pathway described above needs to be determined in future studies.

Neuroendocrinological modulation of social anxiety

Regulation of social anxiety by neurotransmitters such as dopamine (Cervenka et al., 2012; Gunaydin et al., 2014; Shin et al., 2018; Zanettini et al., 2010) and neuroendocrine factors such as OT, AVP, T, and E2 (Borie et al., 2021; Clipperton-Allen et al., 2012; Liu et al., 2021; Murakami et al., 2011; Tsuda et al., 2014; Zoicas et al., 2014) has been widely studied. However, as stated below, it is still not well understood regarding the role played by the LS in neuroendocrine regulation of social anxiety. In this section, therefore, we first overview studies examining how social anxiety is controlled by OT, AVP, T, and E2 through their action on various brain regions. We then discuss possible involvement of the LS in social anxiety modulation.

Role of oxytocin and vasopressin in social anxiety and possible involvement of the LS

OT has been recognized as a hormone that promotes social boning in humans, since intranasal administration of OT increases social trust (Kosfeld et al., 2005). Likewise, a number of animal studies

have reported that OT plays a major role for the control of affiliative behavior (Calcagnoli et al., 2014; De Jong et al., 2014) as well as social anxiety (Murakami et al., 2011; Lazzari et al., 2013). Unlike OT effects on promoting affiliative behavior, effects on control of social anxiety levels are controversial. Male mice showing low levels of social anxiety had higher levels of OT mRNA in the PVN and OTR mRNA in the MeA, compared to male mice showing high levels of social anxiety (Murakami et al., 2011), suggesting that OT functions as anxiolytic for social anxiety. On the other hand, social anxiety levels were lower in OT KO male mice compared to WT mice (Lazzari et al., 2013). Moreover, levels of social anxiety were positively correlated with amounts of OTR mRNA in the LSD in female mice (Clipperton-Allen et al., 2012). These findings suggest a possibility that OT, by acting on OTR in the LS, functions as anxiogenic on social anxiety.

AVP has also been shown to be involved in the control of social anxiety by acting on a number of different brain regions. Amounts of AVP mRNA in the PVN and V1aR mRNA in the MeA were higher in male mice with lower social anxiety (Murakami et al., 2011). In addition, since both investigation toward 'social' stimulus and level of AVP in the CSF were increased by compression of the pituitary stalk in male rats, it suggests that high level of AVP may lower social anxiety levels, which was seen by higher social investigation (Haller et al., 1996). Furthermore, ablation of AVP expressing neurons in the PVN and BNST increased social anxiety in mice (Rigney et al., 2019, 2021a, 2021b). These findings suggest anxiolytic action of AVP for social anxiety. Unlike OT, however, nothing is reported about AVP action in the LS, in relation of social anxiety.

It is worth mentioning that in the LS, OT and AVP are shown to contribute to social memory which is assumed to be affected by animals' social anxiety levels (Horiai et al., 2020; Lukas et al., 2013; Mesic et al., 2015). OT release was increased during memory retrieval, compared to memory acquisition in male rats (Lukas et al., 2013). Social memory in three-chamber social discrimination test in male mice was blocked by OTR KD in the LS using an AAV-mediated cre-loxP system (Mesic et al., 2015). Deficits of social memory in autism spectrum disorder (ASD) mice model was recovered by chemogenetic activation of OTR expressing neurons in the LS (Horiai et al., 2020). Thus, OT signaling via OTR within the LS may facilitate social memory. Recently, AVP signaling was also suggested to control social memory. MAGE family member L2 (MAGEL2) KO mice are known to show impaired social memory as indicated by a lack of preference toward novel social stimulus. In these mice, infusion of AVP into the LS restored social memory (Borie et al., 2021).

Role of testosterone and estradiol in social anxiety and possible mechanisms of action

In humans, social anxiety and social phobia, which are major symptoms of anxiety disorder, is known to be regulated by gonadal steroid hormones (for review, see McHenry et al., 2014). Particularly, T signaling greatly contributes to the control of social anxiety in both sexes. Indeed, it is known that men with elevated levels of social anxiety caused by social defeat experience had lower testosterone levels than healthy controls (Maner et al., 2008). Also. women with symptoms of psychiatric disorder, including social phobia, had lower testosterone levels than healthy participants (Giltay et al., 2012).

Similarly, control of social anxiety by T has been examined in animal models. T acts through both AR and ERs, after being converted to estradiol in the brain. It has been shown that ER signaling pathways play an important role in the regulation of social anxiety. In male mice showing low levels of social anxiety, ERα mRNA in the MeA was much higher than mice with high social anxiety (Murakami et al., 2011). It is also known that elevation of social anxiety induced by maternal diabetes was recovered by infusion of ERβ lentivirus into the amygdala in male mice (Liu et al., 2021). These results suggest that T may exert anxiolytic regulation on social anxiety by acting via ERα and ERβ, rather than AR in male mice.

As discussed above, the LS is known to play a role in reducing the levels of social anxiety (Kask et al., 2001; Shin et al., 2018). However, unlike in the MeA, steroid hormonal regulation of social anxiety in the LS is poorly understood. In the LSD, negative correlation between levels of social interaction and

expression of both ERα and ERβ has been reported in female mice (Clipperton-Allen et al., 2012). If lower levels of social interaction are due to higher levels of social anxiety, this finding can be interpreted as both ERα and ERβ producing anxiogenic effects in the LSD. However, in male rats, infusion of EB into the LS decreased anxiety-like behavior in non-social contexts (Olivera-Lopez et al., 2008), although it was not specified in this study whether E2 acted on ERα or ERβ. In the LS, the number of ERβ expressing neurons in male mice is almost 2.5 times higher than ERα expressing neurons (Hasunuma et al., 2021). In addition, it has been suggested that estrogenic action through ERβ may have anxiolytic effects by a number of studies using ERβ KO mice (Krezel et al., 2001; Tomihara et al., 2009; Tsuda et al., 2014). Thus, gonadal steroid hormones may exert anxiolytic effects on social anxiety in the LS by acting on ERβ. Along this line, it may be worth mentioning a possible association with dopaminergic regulation of social anxiety in the LS. Dopamine signaling via Drd3 is involved in social anxiety. Although it is not directly examined whether Drd3 and ERβ are co-expressed in the LS neurons, both are known to be highly localized in the rostral to medial part of the LSI (Hasunuma et al., 2021; Shin et al. 2018). Therefore, it is conceivable that ERβ mediated estrogenic action on Drd3 may play a role in the control of social anxiety in the LS.

Summary and conclusions

In this review, we have discussed the function of the LS in aggressive behavior and social anxiety. Since inhibitory neurons occupy almost 80% of the LS, activation of GABAergic neurons may be involved in LS regulation of aggressive behavior and social anxiety. Also, LS neurons regulate these behaviors by receiving inputs from a number of brain areas such as the dHIP, vHIP, PVN, and VTA (Figure 1-A). Furthermore, recent optogenetic studies revealed that output from the LS to the VMH contributes to aggressive behavior and that the AHA may regulate social anxiety (Figure 1-B). Therefore, integration of social information in the LS may serve as one of the key elements in neuronal circuits for the control of aggressive behavior and social anxiety.

In the LS, several neuroendocrinological factors and their receptors are expressed. Among them, we have discussed the roles of OT, AVP, T, and E2. Generally, OT inhibits aggressive behavior by acting on OTR, whereas, AVP promotes aggressive behavior via V1aR and V1bR. In the LS, facilitation of aggression by AVP through V1bR is identified, however, the role of OT as well as V1aR-mediated AVP action have not been clarified yet. As for social anxiety, inhibitory effects of both neuropeptides are determined in humans and animal studies. Whereas, in the LS, relationships between these peptides and social anxiety are poorly understood.

Gonadal steroid hormones, T and E2, regulate several social behaviors by acting on AR, ERα and/or ERβ. Behavioral analysis in gene KO mice revealed that activation of AR and ERα promote while ERβ suppress aggressive behavior. In the LS, expression of all three types of receptors and their involvement in the regulation of aggressive behavior have been reported. Higher degree of AR and ERα expression is associated with higher levels of aggressive behavior, whereas ERβ expression is associated with suppression of aggressive behavior. Nonetheless, direct evidence of the relationship between hormonal actions through these receptors and aggressive behavior is still missing. Analysis with brain site specific KD and/or manipulation of neuronal activity of AR, ERα and ERβ positive LS neurons is necessary. In contrast to aggressive behavior, steroid hormone regulation of social anxiety has not been well studied, especially in the LS. However, since dopaminergic regulation of social anxiety via Drd3 in the LSI has been reported, we have proposed possible mechanisms of action of gonadal steroids on social anxiety, i.e., ERβ-mediated genomic action on Drd3.

Finally, in this review, we have not discussed interactions between peptide hormones (OT and AVP) and gonadal steroids (T and E2). As part of genomic action of T and E2, not only synthesis of OT and AVP, but also their receptor expression can be regulated. Therefore, it is necessary to carefully delineate functional significance of these interactions to fully understand neuroendocrine regulation of the brain network for aggressive behavior and social anxiety.

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