Functions of medial hypothalamic and mesolimbic dopamine circuitries in aggression

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Aggression is a crucial survival behavior: it is employed to defend territory, compete for food and mating opportunities, protect kin, and resolve disputes. Two highly conserved circuitries emerge as critical substrates for generating and modulating aggression. One circuitry centers on the medial hypothalamus, a brain region essential for driving the expression of aggressive behaviors. The other circuit involves the mesolimbic dopamine cells. Animal studies support essential roles of mesolimbic dopaminergic signaling in assessing the reward value of aggression and reinforcing aggressive behaviors. In this review, we will provide an overview regarding the functions of medial hypothalamus and dopaminergic system in mediating aggressive behaviors and the potential interactions between these two circuitries.

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Hypothalamic control of aggressive behaviors

The role of the hypothalamus in the generation of aggression is well-established through decades of work in many species. Since the initial work by Walter Hess demonstrating that aggression could be elicited by electrical stimulation in the cat hypothalamus [1], dozens of studies have replicated this result and demonstrated that hypothalamic stimulation is effective in inducing attack or other aggression-related behaviors [2••,3–10,11••,12••,13••,14•,15,16] (Table 1). For example, in marmosets and macaques, electric stimulation of the ventromedial hypothalamus elicited threating vocalization and short attacks [4,5], while in cats, electric stimulation of medial hypothalamus evoked immediate hissing, piloerection and paw strikes towards another cat (https://www.youtube.com/watch?v=Kj2MqEMpj4U) [6,10]. In rats, a large hypothalamic attack area (HAA) from which an attack could be artificially elicited was mapped using systematic micro-stimulation [2••,7,17]. Pharmacological manipulation of the hypothalamus can also facilitate aggression. Ferris et al. injected vasopressin into the anterior hypothalamus of the hamster and observed increased aggressive behaviors [9]. More recently, by capitalizing on advances in mouse genetics and cell-type specific manipulation, a series of studies from our lab and others identified a subnucleus in the medial hypothalamus, the ventrolateral part of the ventromedial hypothalamus (VMHvl), as an essential locus for aggression in both male and female mice [11••,12••,13••,14•]. Optogenetic activation of the VMHvl cells, especially those expressing estrogen receptor alpha/progesterone receptor (overlap nearly 100%), induced immediate attack whereas either pharmacogenetic or optogenetic inactivation of the VMHvl suppressed naturally occurring aggression [11••,12••,13••,14•,18]. in vivo electrophysiological recording revealed that single units in the VMHvl exhibit an acute activity increase both while animals investigate aggression-provoking olfactory cues and during inter-male aggression [11••,19–21,22••,23].

Recent experiments have also confirmed that the role of the hypothalamus during aggression extends beyond acute attack. Early microstimulation experiments demonstrated that hypothalamic stimulation can promote approach towards a potential attack target [24], suggesting the involvement in the preparatory or appetitive aspects prior to aggression. To specifically test the role of VMHvl in promoting preparatory or aggression-seeking behaviors, our recent study adopted an operant responding task to temporally separate the seeking and action phases of aggression. During the task, the animal learns to nose poke to gain access to a weaker intruder. Over 60% of animals learned the task, exhibited repeated poking of the intruder-paired port and attacked intruder immediately upon its introduction. Inactivation of the VMHvl decreased the poking rate whereas optogenetic activation of the VMHvl during inter-poke-interval shortened the latency to the next poke. Furthermore, in vivo recording demonstrated that the VMHvl activity prior to and during poking gradually increased over the days of training as the animals learned the task [23]. These results suggest the involvement of the VMHvl in generating learned seeking or preparatory behaviors in addition to attack.

Table 1

A summary of hypothalamic activation induced aggressive behaviors in various mammalian species

Species	Manipulation	Effect	Reference
Rat	Electrical stimulation	Increase attack	Kruk et al. [7]
			Lammers et al. [15]
			Siegel et al. [2••]
Opossum	Electrical stimulation	Biting attack	Roberts et al. [8]
Cat	Electrical stimulation	Threat, biting attack	Hess [1]
			Egger and Flynn [6]
			Siegel and Pott [10]
Marmoset	Electrical stimulation	Vocal threat and short attacks	Lipp ad Hunsperger [5]
Squirrel monkeys	Electrical stimulation	Biting attack	Renfrew [16]
Macaque	Electrical stimulation	Aggressive vocalization	Robinson [4]
Hamster	Arginine vasopressin	Increase attack	Ferris et al. [9]
Mouse	Optogenetic stimulation (ChR2)	Increase attack	Lin et al. [11••], Lee et al. [13••], Hashikawa et al. [14•,21]
	Pharmacogenetic stimulation (Gq-DREADD)	Increase attack	Yang et al. [18]

A neural circuits approach to research on social behavior has revealed that the VMHvl is embedded within a larger amygdalo-hypothalamic circuit whose nodes have distinct roles in aggression (Figure 1). Here we will summarize the roles of other nodes within this extended circuit that project to the VMHvl. First, the medial amygdala is often referred to as the 'olfactory' amygdala due to the massive converging inputs from the accessory and main olfactory systems [25,26]. It projects to the VMHvl both directly and indirectly via the bed nucleus of stria terminalis [27]. Optogenetic activation of GABAergic neurons but not glutamatergic neurons in the medial amygdala, is sufficient to driving attack in male mice [28]. Optogenetic inactivation of medial amygdala GABAergic cells or permanent ablation of a subpopulation of GABAergic cells expressing aromatase reduces inter-male aggression [28,29]. Second, the ventral premammilary nucleus (PMv) is situated posterior to the VMHvl and provides strong glutamatergic inputs to the VMHvl [30,31]. It receives strong inputs from the medial amygdala and thus is highly responsive to conspecific olfactory cues [31–33]. Lesioning the ventral premammilary nucleus significantly reduces maternal aggression and intruder-induced Fos expression in the VMHvl [32]. Most recently, Stagkourakis et al. found that optogenetic activation of dopamine transporter (DAT) expressing cells in the PMv can elicit attack in spontaneously aggressive, but not non-aggressive, male mice, suggesting a role in enhancing aggressive behaviors [34]. Third, neurons in the subparaventricular zone regulate aggressive behaviors through monosynaptic and disynaptic projections to the VMHvl [35]. It is a major postsynaptic target of the suprachiasmatic nucleus (SCN) which is an important brain region for controlling circadian rhythm [36]. Todd et al. found that VMH-projecting subparaventricular zone GABAergic cells show low activity during early night when the aggression level is high and high activity during early day when the aggression level is low [35].
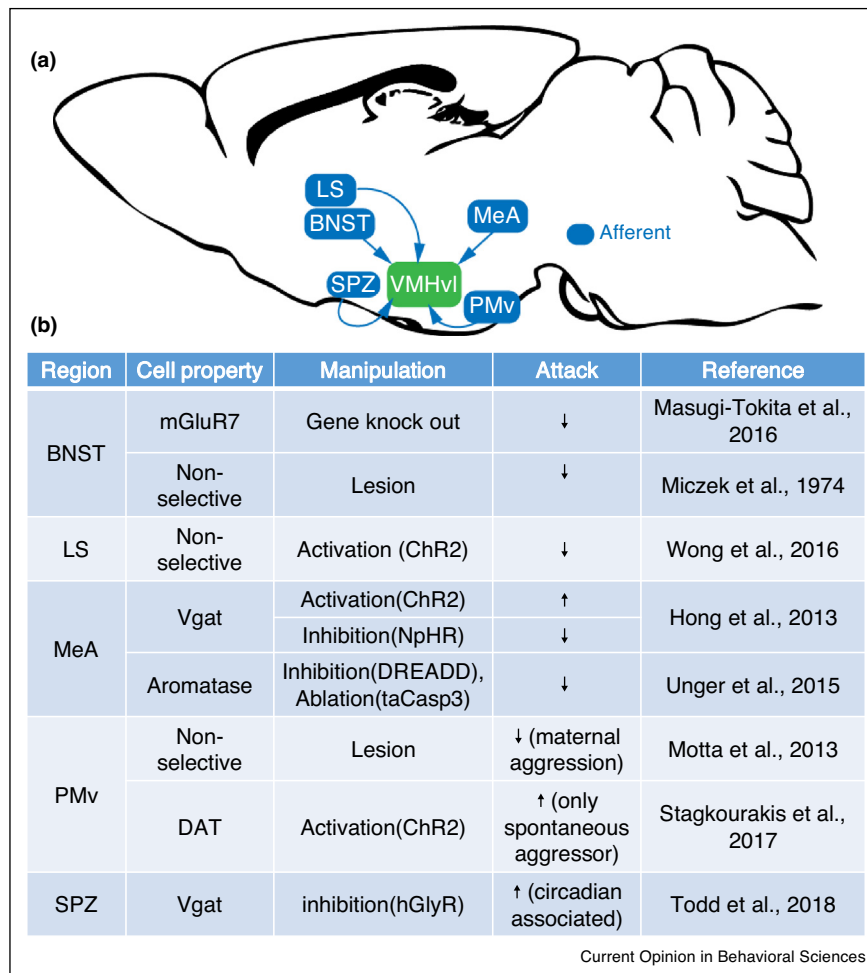
Pharmacogenetic inhibition of subparaventricular zone GABAergic cells increased aggression during early day but not early night. The subparaventricular zone GABAergic projection to the VMH is essential for controlling the daily rhythm of aggression. Fourth, the lateral septum is another source of inhibition to the VMHvl [37]. Lesions in the septum cause an increase in aggression, a phenomenon commonly referred to as 'septal rage' [38]. Interestingly, we found that the lateral septum inhibited attack-excited cells while it activated attack-inhibited cells in the VMHvl, suggesting that lateral septum input has a net effect on suppressing VMHvl activation during aggression. When the pathway from the lateral septum to VMHvl was activated optogenetically, inter-male aggression was significantly reduced [37].

Decades of lesion and electric stimulation studies in a variety of species established an essential role of medial hypothalamus in generating aggressive behaviors. Recent circuit map studies in mice confirmed these earlier findings and provided a more detailed view regarding the medial hypothalamic aggression circuit. Altogether, these works have now established the VMHvl and its connected regions as key neural substrates for generating aggressive behaviors in mice and beyond.

Mesolimbic dopamine control of aggressive behaviors

A parallel set of studies strongly support an essential role of dopaminergic signaling in modulating aggression [39] (Figure 2). To begin, dopamine antagonists represent the most frequent and enduring treatment for suppressing human aggression. Haloperidol, a D2 receptor antagonist, has been used for decades to control aggressive behaviors associated with a wide range of psychotic conditions [40–46]. However, the effect of haloperidol in decreasing aggression is closely linked to the sedative effects caused by the drug, making it a less than ideal

Figure 1

The upstream regions of the VMHvl and their influences on aggressive behaviors. **(a)** Brain regions that provide inputs to the VMHvl. **(b)** A summary of functional manipulations of the upstream areas of the VMHvl during aggressive behaviors. BNST, bed nucleus of stria terminalis; MeA, medial amygdala; PMv, ventral premammillary nucleus; VMHvl, ventromedial hypothalamus ventrolateral part; LS, lateral septum; SPZ, subparaventricular zone; DAT, dopamine transporter; mGluR7, metabotropic glutamate receptor 7; Vgat, Vesicular GABA Transporter.
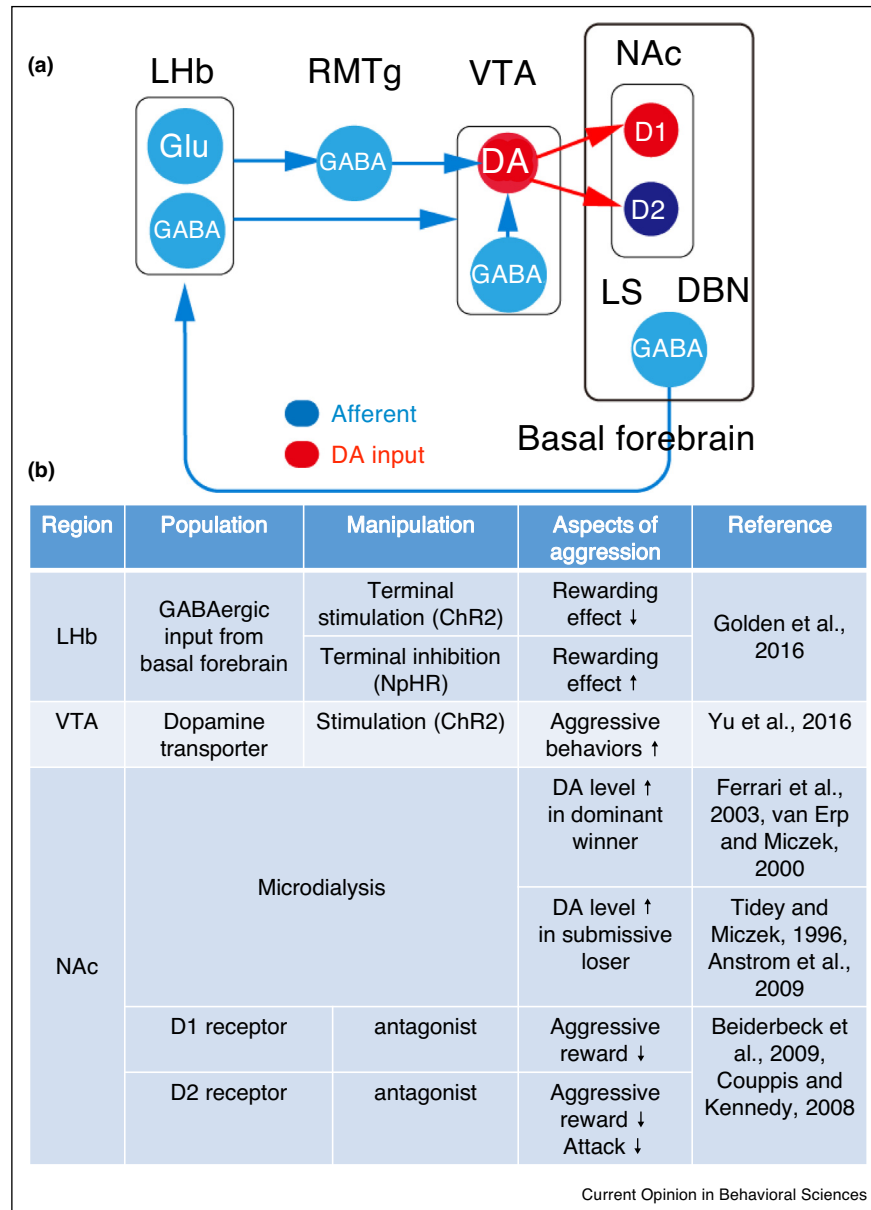
treatment. Other D2 receptor antagonist, such as risperidone, and D1/D2 combined antagonist, Zuclopenthixol, were also found to be effective in suppressing aggression in autistic adults, schizophrenia patients and children with bipolar disorders [47–49]. Consistent with effects in humans, systemic injection of dopamine receptor antagonists in rodents are effective in reducing attack [50,51]. However, the effect of dopamine receptor agonists on aggression varies from study to study [52–54] although methamphetamine, a drug that increases the dopamine release by reversing the DAT action, consistently facilitated aggression [55,56].

More region-specific manipulation of dopamine signaling has revealed that the mesolimbic dopamine pathway (the connection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc)) is the key circuit for controlling aggression. The most direct evidence comes from a recent study by Yu *et al*. In this study, they crossed DAT-Cre mouse line with a Cre-dependent channelrhodopsin reporter line and found that light activation of VTA in those mice significantly enhanced attack towards both male and female intruders [57•]. It is worth noting that in Yu's study, the pulsed blue light was delivered continuously during the 10-min interaction between the test mouse and the intruder. Thus, it is possible that the VTA activation increases attack by enhancing the perceived rewarding value of aggression or in other words aggressive motivation instead of eliciting time-locked attacks as hypothalamic stimulation does.

The role of the mesolimbic dopaminergic pathway in the rewarding effect of aggression was specifically assessed

Figure 2

(a)

(b)

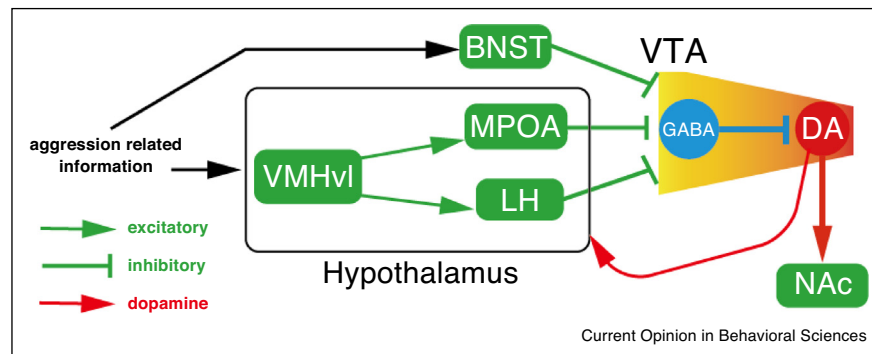| Region	Population	Manipulation		Aspects of aggression	Reference
LHb	GABAergic input from basal forebrain	Terminal stimulation (ChR2)		Rewarding effect ↓	Golden et al., 2016
		Terminal inhibition (NpHR)		Rewarding effect ↑	
VTA	Dopamine transporter	Stimulation (ChR2)		Aggressive behaviors ↑	Yu et al., 2016
NAc	Microdialysis			DA level ↑ in dominant winner	Ferrari et al., 2003, van Erp and Miczek, 2000
				DA level ↑ in submissive loser	Tidey and Miczek, 1996, Anstrom et al., 2009
	D1 receptor	antagonist		Aggressive reward ↓	Beiderbeck et al., 2009, Couppis and Kennedy, 2008
	D2 receptor	antagonist		Aggressive reward ↓ Attack ↓	

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The mesolimbic dopamine system controls the rewarding effect of aggression. **(a)** The potential neural circuit modulates aggressive behaviors through mesolimbic DA signaling. **(b)** A summary of functional manipulation and recording of mesolimbic and relevant areas during aggressive behaviors. DBN, diagonal band nucleus; LHb, lateral habenula; LS, lateral septum; NAc, nucleus accumbens; RMTg, rostromedial tegmental nucleus; VTA, ventral tegmental area; D1, dopamine 1 receptor; D2, dopamine 2 receptor; GABA, GABAergic; Glu, glutamatergic, DA: dopaminergic cells.

using an operant learning paradigm. In a study by Couppis and Kennedy, they trained the male mice to nose poke to gain access to a weak male intruder using a variable ratio (VR-5) schedule [58•]. Under this schedule, the animals were 'rewarded' after 5 pokes on average although the exact number of pokes to trigger the reward varies from trial to trial. In well-trained animals, the authors injected D1 or D2 receptor antagonist into the NAc and found that both D1 and D2 receptor antagonists significantly reduced nose-poking rate at dosages that did not compromise locomotion. Under those dosages, the aggressive behaviors during intruder encounters were only mildly impaired (decrease biting events by 10%). Consistent with findings in mice, D2 receptor antagonist in the NAc suppressed aggression in hyper-aggressive low-anxiety rats [59]. These animal studies are well collaborated with human results, supporting a role of D2 antagonists in suppressing aggressive behaviors.

Figure 3

The hypothalamus and BNST can potentially activate the DA neurons in the VTA through a di-synaptic disinhibition mechanism. The VMHvl projects heavily to the MPOA and LH which are all enriched in GABAergic cells and preferentially target onto the GABAergic cells in the VTA. Activation of the VMHvl glutamatergic cells (~95%) presumably activate the LH and MPOA cells which in turn inhibit the GABAergic cells and then activate the DA neurons in the VTA. BNST also receives aggression-related information and may relay the signal to the VTA dopamine neurons through a similar dis-inhibition mechanism. BNST, bed nucleus of stria terminalis; LH, lateral hypothalamus; MPOA, medial preoptic area; NAc, nucleus accumbens; VMHvl, ventromedial hypothalamus ventrolateral part; VTA, ventral tegmental area; GABA, GABAergic cells; DA, dopaminergic cells.

Several lines of evidences support a role of dopamine in reinforcing aggressive behaviors after winning experience. Systemic injection of either D1 or D2 receptor antagonists after winning blocked the winning induced increase in aggression [60]. Consistent with these functional data, the natural dopamine in NAc was found to reach its peak value 20–30 min following repeated aggression [61•,62•]. The winning induced change in aggression circuit may partly occur in the mesolimbic dopamine pathway itself. After the mice won contests for 20 consecutive days, the mesolimbic VTA tyrosine hydroxylase (TH) and DAT mRNA levels increased and this increase persisted up to 14 days following the last win [63]. The winning-induced increase in aggression could be mimicked by artificial increase in dopamine. Repeated systemic injections of methamphetamine, increased aggression 15 min and 20 hours later [64]. The sustained increase in aggression 20 hours after the drug application is particularly interesting as it supports a role of high level of dopamine in altering the aggression circuit to cause long-term shift in aggressive behaviors. An additional line of evidence that supports a role of the VTA in mediating the rewarding effect of winning comes from studies of an upstream region of the VTA, the lateral habenula (LHb). LHb projects densely to the rostromedial tegmental nucleus (RMTg) which in turn inhibits the dopaminergic cells in the VTA [65,66]. Activation of the LHb terminals suppresses 90% of VTA dopamine neurons [67]. Golden *et al.* used a place preference conditioning paradigm to demonstrate the rewarding value of winning: after aggressive mice attacked and subordinated an intruder, they developed a preference for the intruder-paired chamber. When the LHb was artificially activated by optogenetically silencing an inhibitory input to the LHb, the rewarding effect of winning was blocked [68••]. Thus, reducing activity of the LHb which presumably increasing activity of VTA dopamine neurons is essential for the rewarding effect of winning.

The aforementioned results suggest that one major function of the mesolimbic dopamine is to signal the rewarding value of future or past aggressive behaviors. A decrease in reward expectancy of future attacks decreases actions leading to attack. A high reward after winning experience reinforces future aggressive behaviors. Whether the dopamine signaling in the NAc plays a role in acute execution of attack awaits to be investigated in future studies.

Interaction between the VTA and hypothalamic aggression circuit

The medial hypothalamus and mesolimbic dopamine systems are likely not operating independently. They are several routes for potential interaction, allowing these two circuits to work synergistically to mediate aggression (Figure 3). While the VMHvl projection to the VTA is relatively sparse, VMHvl projects densely to the medial preoptic area (MPOA) and lateral hypothalamus, which in turn project moderately to the VTA [72,73]. Our recent study in female mice found that cells in the MPOA provide inhibitory inputs to virtually 100% non-dopaminergic, presumably mainly GABAergic, cells in the VTA [74]. Since VTA GABAergic cells inhibit dopaminergic cells, inputs from the MPOA to the VTA is expected to disinhibit the dopaminergic cells [75]. Indeed, McHenry *et al.* showed that optogenetic activation of the MPOA neurotensin expressing cells result in time-locked release of dopamine in the NAc [76]. Similarly, the lateral hypothalamus has also been shown to target VTA GABAergic cells and activation of lateral hypothalamic inputs to the

VTA causes dopamine release in the VTA [77]. Thus, there are anatomical connections from the VMHvl to VTA to allow information transfer. Future studies combining simultaneous recordings at VTA and medial hypothalamus and pathway specific inhibition during aggressive behaviors will help address which aspects of aggression-related information may be relayed from the medial hypothalamus to the VTA.

Aggression related information may also be relayed to the VTA through structures upstream of the VMHvl, such as BNST [78]. BNST is a heterogeneous structure containing over 12 subnuclei [79]. While the anterior BNST has been mostly indicated in anxiety and strongly interconnected with central amygdala, a critical region for coping threat, the posterior BNST is strongly interconnected with medial amygdala and likely processes social information [80]. Both anterior and posterior BNST also have access to pheromone information via direct inputs from the accessory olfactory bulb [81]. When the BNST is impaired either by lesion or by gene knockout, the aggression level decreases [82,83]. So far, the function of the BNST to VTA projection has only been examined in the context of anxiety. It was found that BNST cells preferentially target the TH negative cells, presumably GABAergic interneurons in the VTA. The glutamatergic projection from the BNST to the VTA is anxiogenic while the GABAergic BNST projection to the VTA is anxiolytic [84]. The role of BNST in relaying aggression related information to the VTA remain to be investigated in future studies.

The dopamine release, possibly promoted by the hypothalamic neuron activation, can in turn facilitate the excitation of the hypothalamic neurons that drive attack. In a series of electric stimulation studies, it was found that systemic administration of methamphetamine or apomorphine (D2/D1 receptor agonist) decreases the thresholds for hypothalamically elicited rage responses in cats whereas haloperidol (D2 receptor antagonist) elevated the defensive rage threshold [85,86]. When D2 receptor antagonist, but not D1 receptor antagonist, is injected prior to apomorphine, the facilitating effect of apomorphine was blocked, suggesting that the facilitating effect of dopamine on aggression is through D2 receptor [87]. In a follow-up study with more targeted manipulation, apomorphine or a D2 agonist injection into the anterior hypothalamus facilitates hypothalamically evoked rage responses whereas microinjections of D2 antagonist, but not a D1 antagonist, elevated current thresholds to evoke range responses [88]. These results suggest that the dopamine can facilitate attack through its action in the hypothalamus, possibly by acting onto the very hypothalamic cells that drive attacks. Notably, the source of dopaminergic inputs to the hypothalamic attack neurons remain unknown, but likely originated from both within and outside of the hypothalamus, including the VTA [89,90].

Future directions

Decades of research has established essential roles of medial hypothalamus and mesolimbic dopaminergic circuit in aggression. Specifically, the medial hypothalamus appears to be mostly involved in driving both preparatory and consummatory actions related to attack whereas the mesolimbic dopamine system may encode the rewarding value of aggression, either expected or experienced, and modifies the aggression circuit based on winning or losing experience. The medial hypothalamic and mesolimbic dopamine circuit can positively influence each other and several neural pathways have been identified to allow potential interaction. Future studies using pathway specific manipulation and large scale *in vivo* recording will address the pathways, timing and functional roles of the cross-talk between these two systems in more details.

Conflict of interest statement
Nothing declared.

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