Journal Club

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Nucleus Accumbens Dopamine Receptor 1 Expressing Neurons Are Instrumental in Appetitive Aggression

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Review of Golden et al.

Within behavioral neuroscience, aggression is commonly categorized as either reactive, a self-defensive response to perceived threat, or proactive (appetitive), an intrinsic violence-seeking behavior (Moran et al., 2014). The neural mechanisms of appetitive aggression are thought to parallel those involved in drug addiction (Golden and Shaham, 2018). Repeat criminal offenders continue to engage in violent behaviors despite significant adverse consequences (Chester and DeWall, 2016), and they re-offend at a rate comparable to the rates of relapse observed in drug addiction (Durose et al., 2014). Similarly, mice who are repeatedly victorious in violent encounters demonstrate increased aggression seeking, a behavior described as the “winner effect” (de Boer, 2018).

Two interacting circuits in the basal ganglia have been shown to be key in the control of reward and aversion-based learning in mice (Hikida et al., 2010). The nucleus accumbens (NAc), implicated in both the reward component of drug addiction and in the control of reactive aggression (Yamaguchi and Lin, 2018) is central to these. The NAc receives dopaminergic inputs from the ventral tegmental area (VTA) on GABAergic medium spiny neurons. They project both directly and indirectly via the ventral pallidum and subthalamic nucleus, to the substantia nigra pars reticulata, and to the VTA. These interacting direct and indirect circuits control the dynamic balance of the basal ganglia–thalamocortical network and have been shown to be key in the control of reward and aversion-based learning in mice. The majority of striatonigral neurons (the direct pathway) express excitatory D1-type dopamine receptors (Drd1s), whereas the majority of striatopallidal neurons (the indirect pathway) express inhibitory D2-type dopamine receptors (Drd2s; Hikida et al., 2010). It has been shown that Drd1 activation predominantly controls reward-based learning, whereas Drd2 inactivation predominantly controls avoidance (Soares-Cunha et al., 2016a,b). Both circuits are complex, however, and although they appear to have oppositional effects in isolation they can

also act synergistically, and this form of activation may be necessary to efficiently drive positive reinforcement learning (Soares-Cunha et al., 2016a,b).

The role of these circuits in appetitive aggression is comparatively less well understood. Therefore, Golden et al. (2019) studied the involvement of NAc Drd1 or Drd2 type neurons in the control of this behavior, using an “aggression self-administration” task and an “aggression seeking” task. For both, the authors used a previously established operant conditioning protocol, where sexually experienced CD-1 male resident mice were trained to trigger the introduction of a subordinate C57BL/6 male intruder mouse by pressing a lever (Golden et al., 2017). In the self-administration assay, Golden et al. (2019) measured both the total number of lever presses and the number of lever presses leading to attack. Mice were then subjected to an aggression-seeking procedure in which the number of non-reinforced lever presses were measured one day after the last aggression self-administration session.

Golden et al. (2019) reported heightened activation of Drd1 neurons following both tasks. Immunohistochemistry revealed that expression of c-Fos protein, a reporter of neuronal activation, was significantly elevated in the NAc shell (Golden et al., 2019). In addition, *in situ* hybridization revealed that the number of

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neurons coexpressing c-Fos mRNA and either Drd1 or Drd2 mRNA was increased following aggression in the NAc shell and to a lesser extent in the core, suggesting a predominant role for dopamine receptor expressing neurons in the NAc shell in appetitive aggression.

Having demonstrated appetitive aggression related activation of NAc dopamine receptor-expressing neurons, Golden et al. (2019) investigated dopamine receptor subtype contribution by selectively silencing Drd1 or Drd2 neurons using chemogenetics. The authors virally expressed hM4Di, a designer receptor exclusively activated by designer drugs (DREADDs), which usually exerts an inhibitory function, selectively on Drd1 or Drd2 NAc neurons. Behavioral tests for aggression self-administration and aggression seeking were performed within 20 min of hM4Di activation by subthreshold injections of the atypical antipsychotic clozapine. Inactivation of Drd1, but not Drd2, neurons in the NAc significantly decreased the number of attacks and lever presses during the self-administration assay and reduced the persistence of aggression seeking. Therefore, the authors concluded that Drd1 neurons are necessary for the expression of appetitive aggression in mice.

In summary, Golden et al. (2019) have demonstrated that a selective blockade of Drd1 NAc neurons decreases appetitive aggression. This builds upon the findings of Aleyasin et al. (2018a) who identified a unique role of Drd1 neurons in the modulation of aggression. Specifically, Aleyasin et al. (2018a) showed that selective expression of Δ FosB, a transcription factor that regulates a range of reward and motivated behaviors, in Drd1, but not in Drd2 NAc neurons is sufficient to drive an increase in aggression.

Although Golden et al. (2019), or indeed Aleyasin et al. (2018a), have not demonstrated a role for Drd2 neurons in the neurobiology of appetitive aggression, other evidence suggests that these neurons may further enhance Drd1-mediated reward during drug self-administration. Steinberg et al. (2014) showed that administration of a Drd2 antagonist before optogenetic activation of dopaminergic terminals in the NAc attenuated positive reinforcement behavior in rats, and Soares-Cunha et al. (2016a) demonstrated that optogenetic activation of both Drd1 and Drd2 neurons correlates with performance in a motivation-dependent behavioral task. However, both groups noted that Drd2 receptors are also expressed on

NAc cholinergic interneurons, and that selective activation of these interneurons may enhance phasic dopamine release in the NAc, a pathway that could potentiate reward behavior without the involvement of Drd2 medium spiny neurons.

Golden et al. (2019) also provide additional support for the similarity of mechanisms underlying appetitive aggression and drug addiction. The authors showed that Drd1 neuron blockade decreases the expression of aggression seeking following an abstinence period, a behavior resembling relapse behavior in drug addiction, supporting their previous results (Golden et al., 2016, 2017; Aleyasin et al., 2018b; Golden and Shaham, 2018). A similar blockade of Drd1 neurons in the NAc has also been previously shown to impair the acquisition and expression of cocaine-induced conditioned place preference (Hikida et al., 2010). This similarity between cocaine and aggression related circuits is perhaps not surprising. Indeed, both repeated cocaine administration and repeated aggression-related phasic dopamine release induce neural plasticity in basal ganglia circuits by inducing long-term potentiation in striatonigral neurons and long-term depression in striatopallidal neurons (Hikida et al., 2010). Blockade of Drd1 neurons impairs this process (Hikida et al., 2010).

Finally, Golden et al. (2019) indicate that the NAc shell may be more important than the NAc core in the mediation of appetitive aggression. This aligns with previous literature showing that the NAc shell receives inputs from the VTA and projects to the lateral hypothalamus (LH), a region commonly implicated in aggression (Tulogdi et al., 2015). The differential activation between the NAc shell and core is of particular interest because the NAc shell has been previously shown to have a role in formulating the value of reward, whereas the NAc core was associated with motivation to overcome response costs (West and Carelli, 2016). In the study by Golden et al. (2019), the animals did not have to overcome response costs to self-administer aggression. Therefore, it is perhaps expected that their paradigm resulted in increased activity in the NAc shell compared with the core. It would be useful to further investigate whether the activity in the NAc core increases in an intruder self-administration paradigm that includes an increased response cost.

Although this work has advanced our understanding of the cellular basis of appetitive aggression further work is needed to fully understand the circuits involved.

The NAc projects both directly and indirectly to multiple hypothalamic nuclei, including the LH and the ventromedial hypothalamus (VMH; Salgado and Kaplitt, 2015). LH also projects densely to the VTA, perhaps allowing a formation of a circuit loop composed of key aggression related hypothalamic regions, the VTA, and the NAc (Yamaguchi and Lin, 2018). The LH has been previously associated with predatory aggression in rats and cats, and the VMH has been identified as key in the generation of attack behavior. (Tulogdi et al., 2015). The LH receives axon projections from multiple nuclei that have roles relating to appetitive aggression including the arcuate nucleus and the central amygdala. Activation of GABA neurons projecting from the LH to the periaqueductal gray generates appetitive attack (Yamaguchi and Lin, 2018). The LH also has multiple reciprocal connections to the VMH, and recent optogenetic evidence suggests that activity of the VMH neurons is both necessary and sufficient to drive proactive aggression self-administration (Falkner et al., 2016).

In summary, Golden et al. (2019) have proposed a role for NAc Drd1 neurons in the neurobiology of appetitive aggression. In linking the neurobiology of reward and aggression, they add to the growing evidence concerning the addictive component of aggression. The discovery of a cell-type-specific mechanism lays the foundations for further research into the neurobiological origins of pathological aggression, a symptom present in multiple neuropsychiatric disorders. This is a promising step toward developing new treatment strategies.

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