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Optogenetic interrogations of the neural circuits underlying addiction

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Abstract

Exposure to addictive drugs can result in maladaptive alterations in neural circuit function. This review highlights recent progress made in identifying the organization, function, and cellular plasticity of the ventral tegmental area (VTA) and nucleus accumbens (NAc), two brain regions strongly implicated in substance use disorders. Emphasis is given to advances made with new research methodologies, particularly optogenetics, which have provided scientists with an unprecedented ability to map neural circuitry and pinpoint drug-induced synaptic modifications. A better understanding of these adaptive events will aid the development of pharmacological treatments for drug addiction and, more generally, further our understanding of motivated behaviors.

Introduction

The main pathological features of substance use disorders — compulsive drug seeking, loss of self-control, and propensity to relapse — are shared between all classes of addictive drugs. This is suggestive of a common neural mechanism and, indeed, many drug-induced changes in the brain are common to the addicted state.

One of the most prominent effects observed in the brain immediately following drug exposure is an elevation of dopamine (DA) levels, particularly in the NAc [1]. Accordingly, much attention has been devoted to the triggers and consequences of dopamine release, especially in relationship to drug-dependent behaviors [2,3,4•,5]. At the synaptic level, a DA-dependent strengthening of glutamatergic synapses has been observed in both the NAc and VTA after a single *in vivo* exposure to cocaine, as well as other abused drugs [6,7,8•,9]. While it is clear that activity in these two structures has a profound influence on animals' propensity to seek out and work for rewards, research has been hindered by the heterogeneity of cell types and signaling molecules in these regions [10•,11]. In both the NAc and VTA, intermingled populations of cells appear to participate in completely segregated, opposing circuits [12••,13]. Fortunately, advances in experimental techniques, and particularly the development of optogenetics, have now made it possible to stimulate specific cell types and neural pathways with a exceptional degree of spatial, temporal, and neurochemical precision [14]. This review highlights recent studies that have employed these techniques to better understand the circuitry and synaptic modifications underlying substance use disorders (Figure 1) [15–19].

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Optogenetic approaches

Optogenetic techniques capitalize on light-sensitive proteins to control neuronal activity. A wide variety of these proteins have now been optimized for use in neurons, including ion channels and pumps as well as G protein coupled receptors [20,21•,22]. To get selective expression of these proteins, DNA encoding the opsin is introduced into neurons in an anatomically restricted manner, commonly by viral delivery or *in vivo* electroporation [23,24]. Expression of the protein within neurons can be further restricted with the use of selective promoters or DNA recombination systems [25,26]. Once the protein is expressed, it will diffuse within the membrane of cells and over time can be found in distal processes. This allows for the direct manipulation of spiking activity in axons. Thus, there are multiple levels by which photo-stimulation can be restricted: location of DNA delivery, cell-type specific expression, and localized light delivery. When these approaches are used together, anatomically localized, genetically defined neural pathways can be repeatedly stimulated or inhibited, *in vitro* and *in vivo*.

Neural circuitry of the ventral tegmental area

The VTA has a central and complicated role in motivated behaviors [10•]. It is a heterogeneous structure, where DA, GABA, and glutamate projection neurons are all intermingled [27,28]. *In vivo* electrophysiological recordings have been employed in this region to gain insight into when and why these neurons fire, but it has been difficult to unequivocally identify the type of neuron that is, being recorded. Optical tagging refers to the use of optogenetics to determine the identity of neurons during *in vivo* recordings [29,30]. By targeting optical stimulation or inhibition to a specific subset of cells, electrophysiological responses can indicate if the active cell is a neuron that expresses the opsin [31,32•]. This type of approach was recently used to unambiguously identify cell types in the VTA and confirm that it is indeed just DA neurons that signal discrepancies between expected and actual rewards [33••]. Neighboring GABA neurons similarly respond to reward-predicting cues, but their firing pattern is not further modulated in real-time by receipt or omission of the expected reward [33••].

It has long been appreciated that DA plays a major role in reinforcement learning, and now selective photostimulation of VTA DA neurons has confirmed that enhanced activity in these cells is sufficient to reinforce instrumental behavior [34–37]. The firing rate of DA neurons is an important factor, as only high frequency activity patterns can condition a place preference [38]. Selective photo-stimulation of DA neurons is also sufficient to strengthen glutamatergic synapses in the VTA, a consequence common to all addictive drugs [9]. This demonstrates that there is a direct link between DA neuron activity and an increase in the strength of their excitatory synaptic inputs. Whether this plasticity is restricted to specific glutamatergic synapses in the VTA or is a more general phenomenon is still an open question.

An important consideration is that while photostimulation can be highly selective for cell types or pathways, many types of neurons, including DA neurons, release more than one neurotransmitter. Recent optogenetic studies have shown that DA neurons can release glutamate and GABA to varying extents, in addition to DA (Figure 2). While it is presently unclear if these neurotransmitters share the same synaptic vesicles, glutamate release has been observed from dopaminergic axons in the NAc [39–42]. In the dorsal striatum it has been demonstrated that dopaminergic axons scavenge and release GABA [43••]. How widespread these phenomena are among other dopaminergic projections is not yet known. This complexity in the signaling molecules released by DA neurons is part of the reason it

has been so difficult to characterize how the activity of these neurons influences downstream structures [44].

Whether aversive stimuli activate or inhibit different VTA neurons has been another ongoing question, and recent work demonstrates that indeed both effects can occur, just in different, neighboring dopaminergic circuits [33••,45]. One circuit that is, activated by aversive stimuli involves an excitatory projection from the lateral habenula to DA neurons that preferentially innervate the prefrontal cortex (PFC) [12••]. Most of the lateral habenula input, however, inhibits midbrain DA neurons through a GABAergic relay in the rostromedial tegmental nucleus [46•,47,48]. These DA cells, which are inhibited in response to aversive stimuli, preferentially innervate the NAc [48,49]. This is consistent with voltammetry data showing aversive stimuli acutely reduces DA levels there [50,51]. It is unclear if these NAc-projecting DA cells are distinct from those that receive excitatory input from the pedunculopontine tegmentum, which is an input that can generate a conditioned place preference when activated [12••]. These data highlight how neighboring cells can participate in completely segregated circuits. Since inputs to VTA come from all over the brain and outputs go to a similarly wide variety of structures, much more circuit mapping remains to be done here [52••].

Neural circuitry of the nucleus accumbens

The NAc integrates reward-related information from several areas throughout the brain, including the VTA [53]. The principal cell type in the NAc is a GABAergic projection neuron known as a medium spiny neuron (MSN). There are two main types of MSNs and the primary feature that separates them is the direct or indirect route by which they influence neural activity in the midbrain [54]. Optogenetic experiments examining outputs from both the NAc and dorsal striatum have recently provided functional evidence that both direct and indirect output neurons innervate downstream GABA neurons in their respective targeted structures [55,56]. While these studies did not find any evidence for direct pathway innervation of DA neurons, there is strong anatomical evidence that this connection exists [52••,57]. Optogenetic studies have confirmed that MSNs form inhibitory synapses onto each other as well as onto local cholinergic interneurons, but these cells do not synapse on some of the other interneuron populations, such as fast-spiking interneurons [55].

Selective photostimulation of MSN subtypes has confirmed that activity in these cells has opposing influences on behavior, with activity in direct and indirect pathway neurons often encouraging and discouraging behavior, respectively [58]. For example, photostimulation of direct and indirect pathway MSNs in the NAc can bidirectionally alter the ability of cocaine to induce a conditioned place preference [59]. In the dorsal striatum, selective stimulation of MSN subtypes can increase or decrease locomotion, depending on the targeted cell type [31]. These stimulations are also capable of reinforcing or discouraging exploration behavior and can introduce opposing biases in goal-directed action selection [32•,60••]. Likewise, the inhibition of these cell types differentially alters the behavioral plasticity associated with repeated drug treatment [61]. When all MSNs are photostimulated, without regard for subtype, behavioral effects similar to direct pathway stimulation are typically observed. Specifically, photostimulation of all NAc shell MSNs supports intracranial self-stimulation and enhances the rewarding effects of cocaine [59,62••]. Similarly, a place preference is elicited when spiking activity is increased in both MSN populations by photostimulation of G_q-coupled α_{1A}-adrenergic receptors [63].

The influence of cholinergic interneuron populations on behavior has also been explored with selective optogenetic manipulations, and neither activating nor inhibiting these neurons produced gross behavioral effects or elicited a place preference [64]. Inhibiting these

neurons did however increase the firing rate of neighboring cells, and when this was done during cocaine exposure it decreased conditioned place preference [64]. This observation is inconsistent with the finding that indiscriminate activation of all NAc neurons augments cocaine reward, but cholinergic interneuron inhibition may preferentially activate indirect pathway MSNs. These cholinergic inter-neurons can be inhibited in a physiological manner by GABAergic projections from the VTA, which send a remarkably specific input to just these striatal neurons [65•]. Overall the cholinergic interneurons have a very intricate role in modulating NAc physiology, since their photostimulation triggers both DA release and feed-forward inhibition onto MSNs [66–68]. Moreover, these interneurons can also corelease glutamate [69].

Drug-induced synaptic plasticity in the nucleus accumbens

Excitatory input to the NAc primarily comes from the ventral hippocampus, basolateral amygdala, medial pre-frontal cortex, and midline thalamus, and recent optogenetic studies have identified several idiosyncrasies in pathway-specific synaptic properties (Figure 1) [62••]. Innervation patterns are noteworthy as the afferents are heterogeneously distributed and connection strength varies throughout the NAc. Basolateral amygdala inputs are fairly robust throughout the entire ventral striatum, while ventral hippocampal inputs are uniquely localized to and predominate in the medial NAc shell [62••]. Each excitatory input innervates both MSN subtypes but, at least in the dorsomedial NAc core, hippocampal inputs to indirect pathway MSNs are relatively weak [70]. These fibers preferentially innervate small distal spines on indirect pathway MSNs, which makes the hippocampal input to these cells relatively ineffective at driving postsynaptic action potentials. PFC and thalamus inputs, in contrast, similarly innervate both MSN subtypes in the NAc core [70]. The data overall suggest that differences between NAc inputs might be more a matter of degree than categorical. This raises the possibility that the various excitatory inputs have similar ways of engaging striatal microcircuitry. Indeed, photostimulation of different sets of glutamate axons in the NAc, whether they are from the hippocampus, amygdala, or PFC, can similarly reinforce instrumental behavior [62••,71•]. Of course, particular environmental stimuli differentially activate these pathways, but photo-stimulation of each group of axons is sufficient to drive intracranial self-stimulation and induce a place preference. This indicates the information encoded in these inputs has incentive properties and can contribute to reinforcement learning. Determining what exactly is encoded in these specific inputs is an area of ongoing investigation.

Repeated exposure to cocaine initiates a cascade of events in the NAc [72,73]. One particularly intriguing effect that appears a week or two after cocaine use starts is a potentiation of excitatory inputs to MSNs [74•,75]. When cocaine is self-administered under extended access paradigms, this synaptic potentiation involves the insertion of GluR2-lacking AMPA receptors, and blocking these specific receptors can attenuate compulsive drug seeking [76–78]. It is presently unclear if this particular type of synaptic plasticity is localized to specific inputs or cell types in the NAc. However, several pathway-specific synaptic modifications have recently been identified following various drug-administration paradigms. For example, following withdrawal from self-administered cocaine, there is an increase in transmitter release probability in PFC, but not amygdala, inputs to the NAc [79].

Presently, drug-induced, pathway-specific postsynaptic modifications have only been reported after experimenter-administered, intraperitoneal injections of cocaine. With this paradigm, ventral hippocampus inputs in the medial NAc shell are selectively potentiated when compared with basolateral amygdala and prefrontal cortex inputs [62••]. A separate study which distinguished MSN subtypes and focused on PFC infralimbic inputs to the NAc found a selective potentiation of these synapses on direct pathway MSNs [8•]. Intriguingly,

depotentiation of these synapses was effective at reversing cocaine-induced locomotor sensitization [8•]. This parallels what happens with direct optical inhibition of the infralimbic cortex, which is effective at stopping habitual behavior on a T-maze [80•]. Other PFC regions have also been implicated in drug-related behaviors, and optical inhibition of the prelimbic cortex, as well as a more selective inhibition of the prelimbic inputs to the NAc core, blocks cocaine-primed cocaine seeking [81]. Together, these studies raise the possibility that attenuating PFC input to the NAc may be an effective treatment for drug abuse disorders.

Another avenue of research explores if small subsets or ensembles of MSNs are responsible for specific drug-related behaviors. Indeed, only a small minority of MSNs show c-fos activation in response to cocaine exposure [82]. Inactivating these specific cells, which exhibit their own unique drug-induced synaptic modifications, is sufficient in disrupting cocaine-induced psychomotor sensitization [83•,84]. These data highlight the complexity of drug-induced synaptic plasticity and stress the importance of identifying what modifications underlie the pathological features of drug abuse disorders.

Conclusions

Because of the complex assortment of cell types, neurotransmitters systems, and subcircuits within the VTA and NAc, optogenetic techniques have been a boon for research on these structures. Many well-established hypotheses have been confirmed, such as the fact that some DA neurons are activated by aversive stimuli and corelease glutamate [33••,39,41]. Likewise, the opposing forces of the two MSN subtypes in the striatum have been verified, and now we have detailed information on what this means for specific behaviors [31,32•,59]. There have also been many surprises from the use of optogenetic techniques, such as the fact that dopamine neurons can release GABA and that glutamatergic input to the NAc from any number of sources can carry a rewarding signal [43••,62••]. Future research will further benefit from the use of temporally precise optical inhibition to uncover the specific physiological role of different neural circuits. This type of work has already revealed circuits that can attenuate habitual behavior, which is particularly important for the goal of overcoming drug addiction [8•,80•].

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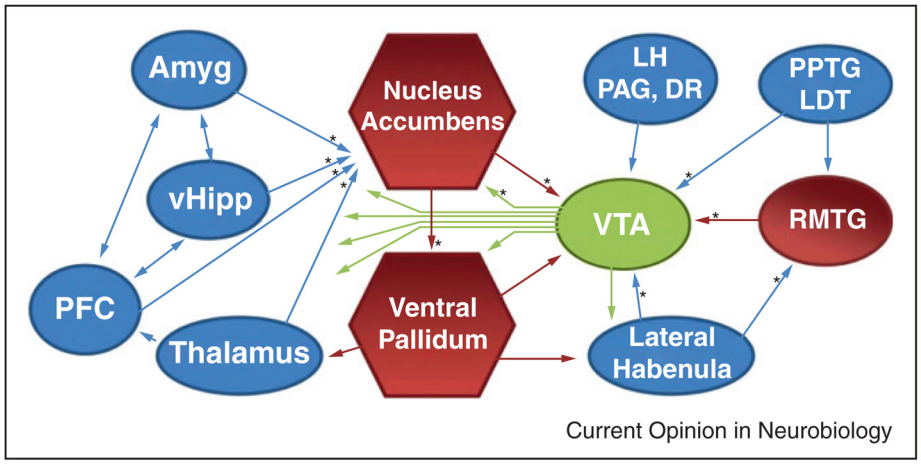

Figure 1.

Schematic of the principal brain regions that innervate the VTA and NAc. Red indicates inhibitory structures and blue indicates excitatory structures. Pathways that have been examined with optogenetic techniques are indicated with an *. Amyg, amygdala; vHipp, ventral hippocampus; LH, lateral hypothalamus; PAG, periaqueductal gray; DR, dorsal raphe; PPTG/LDT, pedunculopontine and laterodorsal tegmentum; RMTG, rostromedial tegmental nucleus.

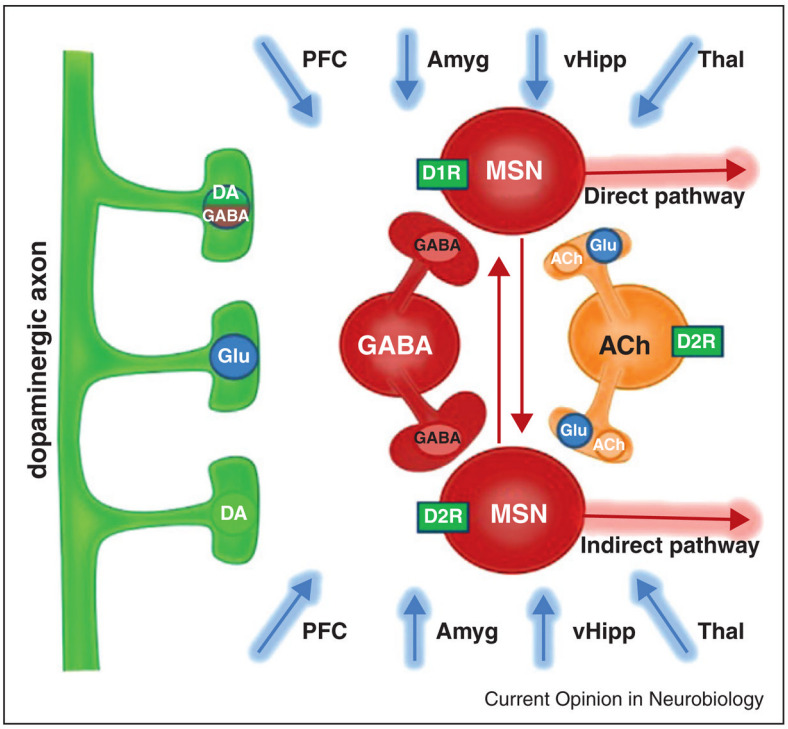

Figure 2.

Schematic of the organization of the nucleus accumbens. Both dopaminergic and glutamatergic fibers innervate each local cell type. Multiple neurotransmitters are released from dopaminergic and cholinergic axons. The two types of MSNs can be differentiated by the dopamine receptors they express and their access to the midbrain, which is either direct or indirect.