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Review

Establishing causality for dopamine in neural function and behavior with optogenetics

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ABSTRACT

Dopamine (DA) is known to play essential roles in neural function and behavior. Accordingly, DA neurons have been the focus of intense experimental investigation that has led to many important advances in our understanding of how DA influences these processes. However, it is becoming increasingly appreciated that delineating the precise contributions of DA neurons to cellular, circuit, and systems-level phenomena will require more sophisticated control over their patterns of activity than conventional techniques can provide. Specifically, the roles played by DA neurons are likely to depend on their afferent and efferent connectivity, the timing and length of their neural activation, and the nature of the behavior under investigation. Recently developed optogenetic tools hold great promise for disentangling these complex issues. Here we discuss the use of light-sensitive microbial opsins in the context of outstanding questions in DA research. A major technical advance offered by these proteins is the ability to bidirectionally modulate DA neuron activity in *in vitro* and *in vivo* preparations on a time scale that more closely approximates those of neural, perceptual and behavioral events. In addition, continued advances in rodent genetics and viral-mediated gene delivery have contributed to the ability to selectively target DA neurons or their individual afferent and efferent connections. Further, these tools are suitable for use in experimental subjects engaged in complex behaviors. After reviewing the strengths and limitations of optogenetic methodologies, we conclude by describing early efforts in the application of this valuable new approach that demonstrate its potential to improve our understanding of the neural and behavioral functions of DA.

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1. Introduction

The neural and behavioral functions of dopamine have been studied using a variety of experimental approaches, including lesioning of DA neurons, application of DA receptor agonists and antagonists, neurochemical measurements of DA concentrations and DA release, and electrophysiological measurements of DA neuronal activity. These and other techniques have been utilized alone and in combination to great effect. But, like all techniques, these methods have some limitations. For example, observance of a behavioral effect after injection of a DA receptor antagonist indicates that endogenous DA actions at DA receptors contribute to that behavioral process. However, the relatively long time course of drug action makes it difficult to relate temporally-specific patterns of DA neuronal activity and release to behavior emitted on short timescales. On the other hand, the precision afforded by electrophysiological recordings from the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc), where the predominant populations of DA neurons reside, allows for tight temporal correlation of these neurons' activity with perceptual events and behavior. However, the ability to demonstrate causality, and neurochemical specificity, has remained limited. Similarly, with *in vitro* slice recording, we can learn much about DA effects upon synapses and circuits, but the afferents that are stimulated are often mixed, limiting conclusions. Here we review the use of optogenetic tools to activate or inhibit the activity of midbrain DA neurons as well as their afferents and efferents in neural slices and in behaving animals, and discuss the advantages provided by these tools for studies that seek to link DA neuronal activity, circuit function, and behavior. To provide context for the discussion of optogenetic approaches, we first briefly review ideas of the role of DA in behavior. We next discuss outstanding questions where further experimentation is needed to elucidate causal roles for dopamine neurons in neural circuit function and behavior. We then discuss the merits and limitations of using optogenetics to address these questions. Finally, we close with a review of exciting recent findings using optogenetic approaches that have successfully begun to address the critical questions raised in the initial sections of this review.

2. Dopamine and behavior

Dopamine neurons in the SNc and the VTA send long-range projections to many sites in the forebrain, with the SNc DA neurons projecting primarily to the dorsal striatum (*i.e.*, the caudate/putamen) and the VTA projecting primarily to the ventral striatum (the nucleus accumbens (NAc) and olfactory tubercle) as well as prefrontal cortex, the amygdala and the hippocampus (Beckstead et al., 1979; Swanson, 1982). Given this broad pattern of efferents, it is not surprising that the