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Warning! Dopaminergic Modulation of the Superior Colliculus

Jaclyn Essig^{1,2} and Gidon Felsen^{1,2,*}

¹Department of Physiology and Biophysics, University of Colorado School of Medicine, Aurora, CO 80045

²Neuroscience Program, University of Colorado School of Medicine, Aurora, CO 80045

Abstract

Recent work by Bolton *et al.* describes a dopaminergic input to the superior colliculus (SC) from the zona incerta, as well as the organization of D1- and D2-receptor expression in the SC. We discuss a potential role for this input in modulating SC-mediated behavior, particularly in response to aversive stimuli.

Keywords

orienting; avoidance; A13; zona incerta

The superior colliculus (SC) is a layered midbrain structure that integrates multimodal sensory input with modulatory input from numerous brain regions in order to select and coordinate orienting movements [1]. The functional role of these modulatory inputs, which are known to include GABAergic and cholinergic innervation, in influencing movement-related SC processing is an active area of investigation [2].

In a recent report [3], Bolton *et al.* identified and described another potential modulatory influence in the SC, via dopaminergic innervation. First, using RNA sequencing in rat SC, Bolton and colleagues revealed high levels of *Drd1a* and *Drd2*, the transcripts that code for D1 and D2 dopamine receptors, respectively. Notably, these transcripts were present at roughly the same levels in their samples as those that code for common glutamate receptors. Next, by examining fluorescence expression in the SC of D1-tdTom and D2-EGFP mice, transgenic lines that label D1- and D2-expressing neurons, they found that these neurons are segregated within the SC: D1-expressing neurons are more commonly localized to the superficial layers, while D2-expressing neurons are primarily found within the intermediate layers. They next asked whether excitatory or inhibitory neurons – the latter comprising nearly one-third of neurons in the SC [4] – preferentially express D1 or D2 receptors. By crossing the above mouse lines with a reporter line (VGAT-Venus), they determined that the

*Correspondence: gidon.felsen@ucdenver.edu (G. Felsen). Phone: (303) 724-4532, Fax: (303) 724-4501, 12800 E. 19th Ave., Mail Stop 8307, Aurora, CO 80045, USA.

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majority of D1-expressing neurons – particularly in the superficial layers – were GABAergic, while the majority of D2-expressing neurons were not. These results suggest that dopamine may play a role in SC processing, and raise two immediate questions: 1) What is the source of dopamine input to the SC, and 2) How does dopamine affect activity in the SC?

Bolton and colleagues addressed the first question using a combination of retrograde labeling and immunohistochemistry to determine which of several known dopaminergic areas project to the SC. Surprisingly, they observed no retrograde labeling in two of the more commonly-studied dopaminergic regions – the substantia nigra pars compacta (A9) and the ventral tegmental area (A10) – but instead found labeling in a dopaminergic subregion of the zona incerta known as A13 (they also observed a small amount of labeling in the locus coeruleus, which is primarily noradrenergic but can co-release dopamine). In support of this finding, dopaminergic terminals in the SC, identified via antibody staining for tyrosine hydroxylase (an enzyme required for dopamine synthesis), did not express the dopamine transporter, which is commonly found in terminals for dopamine reuptake; Bolton *et al.* note that A13 is the only known dopaminergic cell group that does not express the dopamine transporter. The physiological effects of dopamine on D1- and D2-receptor-expressing SC neurons were then isolated via a series of whole-cell recording experiments in acute slices. D1- and D2-expressing neurons were both found to be robustly inhibited by dopamine, demonstrating the physiological relevance of the dopaminergic input that, based on the experiments described above, arises at least in part from A13. Together, these findings raise the question of what role dopaminergic input plays in SC-mediated behavior.

While the SC is critical for orienting movements in general, one line of research has described its specific role in avoiding aversive stimuli and approaching appetitive stimuli (Figure 1) [5]. In rodents, in which aversive stimuli (e.g., predators) often arise from above, the medial SC – which represents the upper visual field – has been shown to mediate avoidance responses, while the lateral SC – which represents the lower visual field – mediates approach responses. Bolton *et al.* demonstrated that, although dopamine receptor expression is robust throughout the mediolateral extent of the SC, dopaminergic A13 neurons innervate the medial SC [3]. Further, while their retrograde tracing experiments do not appear to have examined input to the lateral SC, results from a similar set of experiments that focused specifically on differential innervation of medial and lateral SC suggests that input from A13 may be restricted to the medial SC (whereas other subregions of the zona incerta project laterally) [6]. Therefore, one possible role for dopaminergic input to the SC is to contribute to the avoidance response to aversive stimuli. Notably, A13 also projects to the periaqueductal grey (PAG), another midbrain structure known to promote avoidance behaviors [7] that is reciprocally connected to the SC [1]. These results suggest that A13 input to both the SC and PAG may signal the presence of an aversive stimulus, which could coordinate the activity in these structures that elicits an avoidance response (Figure 1). While this idea is speculative and remains to be tested, a recent study showed that sulpiride, a D2 antagonist, elicits similar avoidance behavior when infused into either the SC or the PAG of rats [8]. These results provide some support for the involvement of dopaminergic signaling in these structures in avoidance behavior.

As is often the case with illuminating studies of the nervous system, the work by Bolton and colleagues has raised at least as many interesting questions as it has answered. For example, how does dopaminergic input modulate SC function in behaving animals? Describing the localization of D1- and D2-expressing neurons, their likelihood of being excitatory or inhibitory, and the physiological effects of dopamine in SC slices are critical first steps. Consistent with the inhibitory effect of dopamine in slice studies [3] and the excitatory effect of a D2 antagonist on avoidance behavior [8], an intuitive idea is that increased dopamine signaling in the SC may inhibit behavioral responses [3]. However, given the numerous specific forms of intra- and inter-layer connectivity that comprise the complex functional circuitry of the SC [9], targeted *in vivo* experiments will be required to test this idea. Related, what drives the activity of dopaminergic A13 neurons? We speculate above that their activity may be related to signaling aversive stimuli, but this idea, too, remains to be tested. Finally, how, if at all, does the function of the dopaminergic input *to* the SC relate to the function of the input to dopaminergic regions *from* the SC [10]? Future studies can build on the work of Bolton *et al.* to begin to address these questions.

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Figure 1. Dopaminergic input to the SC may modulate avoidance behavior

Activity in the medial SC is thought to elicit an avoidance response to an aversive stimulus [5]. This region receives input from A13, a dopaminergic subregion of the zona incerta [3,6]. A13 also projects to another region involved in avoidance, PAG [7,8], suggesting that A13 could play a role in coordinating the response to aversive stimuli. Abbreviations: SC, superior colliculus; PAG, periaqueductal gray.