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Serotonin Subsystems Modulate Diverse and Opposite Behavioral Functions

Alvaro L. Garcia-Garcia*,† and Mariano Soiza-Reilly*,‡

†Department of Psychiatry, Division of Systems Neuroscience, Columbia University and the New York State Psychiatric Institute, 1051 Riverside Dr. Box 87, New York, New York 10032, United States

‡Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE), CONICET, Universidad de Buenos Aires, Buenos Aires Argentina

ABSTRACT: Pioneering work showed that serotonin (5-HT) neurons have the unique capacity to engage in different and opposed aspects of motivated behaviors such as reward and punishment responses. These findings provided strong evidence about the functional heterogeneity of 5-HT neurons, and their possible engagement in multiple and behaviorally distinct neural subsystems. A recent study provides further compelling evidence supporting this notion, in which two ascending 5-HT circuits modulate opposed aspects of motivated behaviors.

KEYWORDS: *5-HT, Reward, Punishment, Frontal Cortex, Amygdala, Optogenetics, Chemogenetics*

The dorsal raphe nucleus (DRN) contains the largest group of serotonin (5-hydroxytryptamine, 5-HT) producing neurons in the brain (approximately ∼9000 neurons in the mouse), sending axon projections to almost the entire forebrain. 5-HT neurons regulate a widespread and diverse array of physiological and behavioral processes, and its dysfunction has been associated with a range of human mental illnesses, including depression and anxiety. Yet, the precise mapping of 5-HT circuits that regulate this diversity of biological functions remains poorly understood. However, the use of recently engineered genetic and viral tools allowed researchers to begin to untangle the complex physiology and function of this small and apparently homogeneous group of cells.

One strategy to investigate the role of DRN 5-HT cells in this diverse repertoire of functions is to measure their activity while animals perform specific behaviors. This has been challenging in the past because only two-thirds of DRN neurons produce 5-HT, while the remaining produce GABA, glutamate or dopamine. Recent studies overcame this, and researchers have recorded the activity of identified DRN 5-HT neurons, distinguishing it from the activity of the neighboring non-5-HT neurons, by selectively "tagging" 5-HT neurons with different viral approaches.[1−3] Specifically, Cohen et al. used the selective expression of the light-sensitive opsin channelrhodopsin-2 (ChR2) in DRN 5-HT neurons, that allows for identification based on the cell responses that are generated after a brief pulse of blue light.[2] Using this approach, it has been shown that identified DRN 5-HT neurons modulate their tonic firing rates over the course of minutes during the reward versus punishment blocks, and that while virtually all DRN 5-HT neurons show phasic firing changes to punishment, approximately half of them display the same changes to reward-predictive cues.[2] Furthermore, two recent studies had combined a viral/genetic strategy with the use of fiber photometry, to express the genetically encoded Ca^{2+} indicator GCaMP6 in DRN 5-HT neurons, for *in vivo* optical monitoring of neural activity.[1,3] Consistent with Cohen et al., both studies showed that rewards of a different nature, such as sucrose, food, sex, and social interaction, rapidly activate DRN 5-HT neurons. However, in response to punishments or aversive stimuli, the DRN 5-HT neurons display divergent responses. Specifically, in one study, 5-HT neurons do not respond to quinine or foot shocks,[3] while in the other 5-HT neurons display more varied responses to foot shocks, including biphasic activity responses involving first a transient augmentation followed by a long-lasting depression.[1] Although these studies considered the DRN 5-HT system as a monolithic whole, their findings suggest that, even within the DRN, 5-HT neurons can have heterogeneous responses to reward and punishment stimuli. We could hypothesize that such functional heterogeneity of 5-HT neurons could be a mere result of recording from different subpopulations of 5-HT cells. Indeed, accumulating anatomical and molecular evidence supports the existence of heterogeneity within the DRN 5-HT neurons. Very recently, using viral-conditional neuronal labeling in combination with whole-mount imaging, it has been shown that DRN 5-HT neurons sending projections to the orbitofrontal cortex (OFC) and to the central nucleus of the amygdala (CeA) are different cell subpopulations with different and largely complementary brain targets[1] (Figure 1). The study shows that DRN 5-HT neurons projecting to the OFC and CeA showed an activation pattern in response to a reward; however, this activation is more robust in the OFC-projecting 5-HT neurons. In contrast, while 5-HT neurons projecting to the OFC show a decreased activity in response to a punishment, CeA-projecting 5-HT neurons display transient increases in their firing activity[1] (Figure 1). Altogether, these

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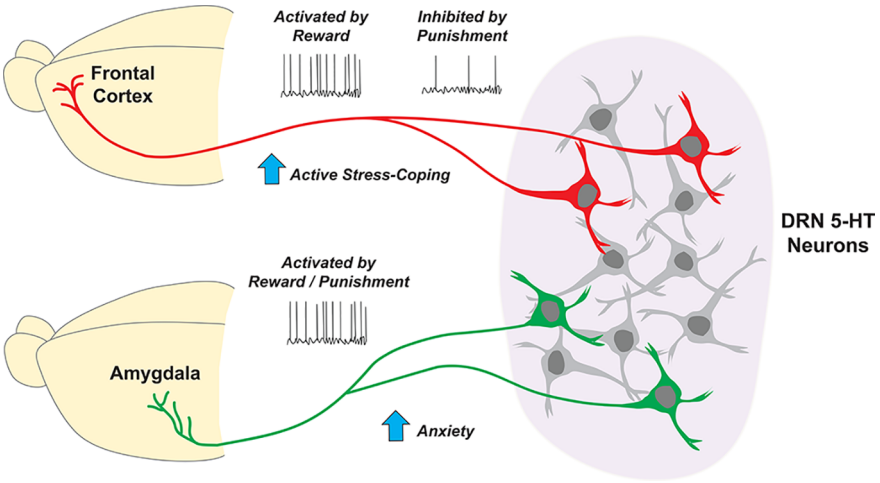

Figure 1. Serotonin (5-HT) subsystems in the DRN with opposite responses to reward and punishment differentially modulate anxiety and stress-coping behavior. A subpopulation of DRN 5-HT neurons sending axon projections to the frontal cortex (in red), including the orbitofrontal region (OFC), are preferentially activated by rewards and largely inhibited by punishment. The other defined subsystem arises from DRN 5-HT neurons projecting to the central nucleus of the amygdala (CeA) (in green). This subpopulation of cells responds actively to both reward and punishment. Pharmacogenetic activation of DRN-to-OFC circuit increases the active stress-coping, while activity of the DRN-to-CeA circuit increases anxiety levels.

results provide compelling evidence suggesting that the apparent heterogeneity of physiological responses of 5-HT neurons to reward and punishment[2,3] may be indeed a direct consequence of recording from 5-HT neurons from different projection-specific subpopulations present in the DRN.[1]

While recent evidence suggests that the DRN 5-HT system is composed of both physiologically and anatomically divergent subsystems, they also suggest that the functional influence of these subsystems would diverge together with their anatomical connectivity. Recent studies have begun to shed some light on this by manipulating the activity of DRN 5-HT subsystems at their targets, to determine their role in shaping behavior. By using pharmacogenetic activation as a gain-of-function strategy, it has been shown that the OFC-projecting 5-HT neurons negatively regulate locomotion, reducing the passive stress-coping responses, without impacting anxiety levels (Figure 1). In contrast, the pharmacogenetic activation of the CeA-projecting DRN 5-HT neurons do not affect the locomotor or stress-coping responses, but increases anxiety levels[1] (Figure 1). In addition, another study using optogenetic activation of 5-HT afferents to the CeA showed that this acute manipulation is not sufficient to affect anxiety levels.[4] This apparent controversy could be likely explained by the efficiency/intensity of the different activation methods. In any case, these results together indicate that while OFC-projecting DRN 5-HT neurons promote active coping, CeA-projecting 5-HT neurons might modulate anxiety-like behaviors, suggesting specific roles for these two DRN 5-HT subsystems in modulating the behavioral function. Interestingly, CeA-projecting 5-HT neurons send axon collaterals to other amygdala nuclei such as the bed nucleus of stria terminalis (BNST),[1] where the optogenetic activation of both raphe and DRN 5-HT neuron inputs in the BNST impact anxiety-related behaviors,[4,5] suggesting that modulation of anxiety-like behaviors involves reciprocal connections between this subsystem of DRN 5-HT neurons, the CeA, and the BNST.

Overall, these studies have started to untangle the complex organization and function of the 5-HT system, providing a more precise and complete picture of it by integrating anatomical and physiological features to behavior. These efforts, together with the recent advances in the molecular characterization and classification of 5-HT raphe neurons, will help to better understand how different circuit-specific 5-HT subsystems modulate behavior. This will contribute in elucidating of how malfunctioning of these circuits could contribute to mental illnesses, paving the way for the development of new and more effective pharmacotherapies to treat them.

AUTHOR INFORMATION

Corresponding Authors

*Mailing address: Department of Psychiatry, Division of Systems Neuroscience, Columbia University and the New York State Psychiatric Institute, 1051 Riverside Dr., Box 87, New York, NY 10032. E-mail: ag3149@cumc.columbia.edu or aggarcia83@gmail.com.

*Mailing address: Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE), CONICET, Universidad de Buenos Aires, Ciudad Universitaria, Pab. 2, 2° piso (C1428EHA), Buenos Aires, Argentina. E-mail: msoizareilly@fbmc.fcen.uba.ar.

ORCID

Alvaro L. Garcia-Garcia: 0000-0003-2133-8062

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Notes

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REFERENCES

(1) Ren, J., Friedmann, D., Xiong, J., Liu, C. D., Ferguson, B. R., Weerakkody, T., DeLoach, K. E., Ran, C., Pun, A., Sun, Y., Weissbourd, B., Neve, R. L., Huguenard, J., Horowitz, M. A., and Luo, L. (2018) Anatomically Defined and Functionally Distinct Dorsal Raphe Serotonin Sub-systems. *Cell 175*, 472.

(2) Cohen, J. Y., Amoroso, M. W., and Uchida, N. (2015) Serotonergic neurons signal reward and punishment on multiple timescales. *eLife 4*, e06346.

(3) Li, Y., Zhong, W., Wang, D., Feng, Q., Liu, Z., Zhou, J., Jia, C., Hu, F., Zeng, J., Guo, Q., Fu, L., and Luo, M. (2016) Serotonin neurons in the dorsal raphe nucleus encode reward signals. *Nat. Commun. 7*, 10503.

(4) Garcia-Garcia, A. L., Canetta, S., Stujenske, J. M., Burghardt, N. S., Ansorge, M. S., Dranovsky, A., and Leonardo, E. D. (2017) Serotonin inputs to the dorsal BNST modulate anxiety in a 5-HT1A receptor-dependent manner. *Mol. Psychiatry*, DOI: 10.1038/mp.2017.165.

(5) Marcinkiewcz, C. A., Mazzone, C. M., D'Agostino, G., Halladay, L. R., Hardaway, J. A., DiBerto, J. F., Navarro, M., Burnham, N., Cristiano, C., Dorrier, C. E., Tipton, G. J., Ramakrishnan, C., Kozicz, T., Deisseroth, K., Thiele, T. E., McElligott, Z. A., Holmes, A., Heisler, L. K., and Kash, T. L. (2016) Serotonin engages an anxiety and fear-promoting circuit in the extended amygdala. *Nature 537*, 97−101.

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