No. PSTR347.03

Serotonergic Regulation of Fastigial Nucleus for Muscle Activity

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Introduction

Switching modes from relaxed to alerted state is essential for survival as it enables rapid responses to threat or danger cues. The serotoninergic system that is important in stress regulation, is also known to play a role in motor regulation. Although the relationship between stress and motor ability has been well known, the biological mechanism of stress-related motor regulation is yet known.

The serotonergic neurons in the dorsal raphe nucleus projects brain-wide, including the cerebellar nucleus, and serotonin enhances motor ability via Htr2A receptors in the cerebellar nucleus. A study (Kim et al., 2021) shows that the photoexcitation of stress-excited serotonergic neurons from the dorsal raphe nucleus at the fastigial nucleus results in dystonic symptom – severe contraction of muscles.

We have used tracing and viral expression methods to observe the function of this circuit. Projection from the dorsal raphe nucleus to the fastigial nucleus were mostly serotonergic with a minority of non-serotonergic neurons. The activation of these neurons altered gaits by increasing stride lengths, which may be important in enlarging movement in stressful or threat situations.

Methods & Materials

1. Retrograde tracing from the fastigial nucleus
2. Neuronal population study in the DRN
3. Viral expression of ligand-dependent muscarinic 3 for neuronal excitation
4. Behavioral analysis of hindlimb movement

Results

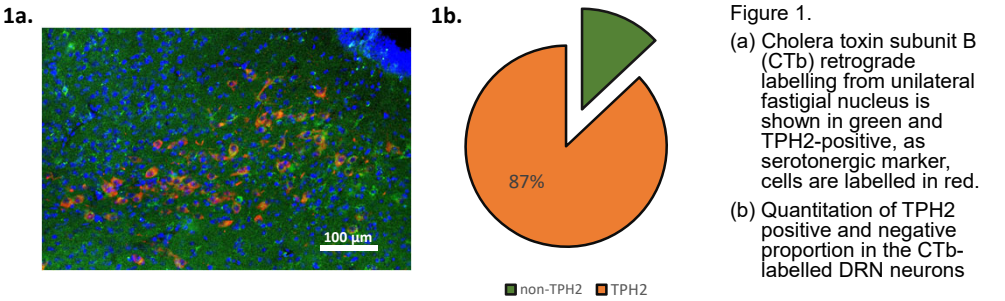

Figure 1.
(a) Cholera toxin subunit B (CTb) retrograde labelling from unilateral fastigial nucleus is shown in green and TPH2-positive, as serotonergic marker, cells are labelled in red.
(b) Quantitation of TPH2 positive and negative proportion in the CTb-labelled DRN neurons

Figure 2.
(a) Adeno-associated virus retrogradely expressing Cre protein was injected in the bilateral fastigial nucleus. (b) Cre-dependent green fluorescence protein expression in the dorsal raphe nucleus in shown in green. The majority population locates in the dorsal and lateral of the dorsal raphe nucleus shown.

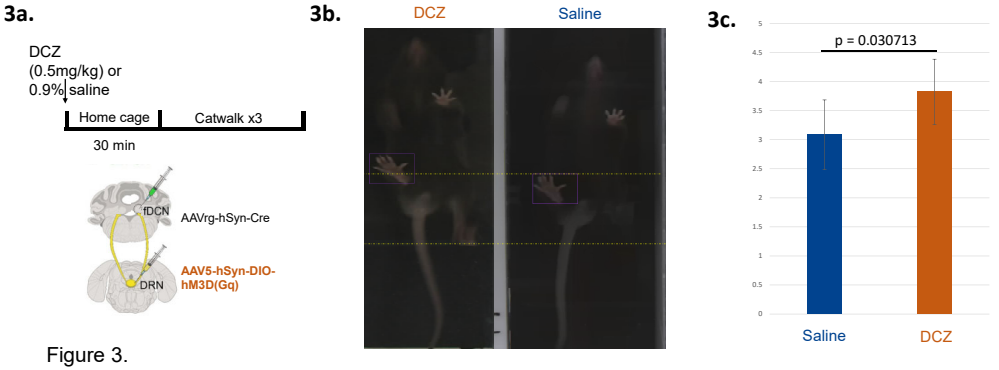

Figure 3.
(a) Scheme for gait analysis of dorsal raphe nucleus excitation tests. (b) Bottom-up view of catwalk session comparing control trial and experimental trial within the same mouse. (c) Stride length of ipsilateral foot to the injected brain.

Discussion

Serotonergic neurons in dorsal raphe nucleus that projects to the fastigial nucleus can regulate motor function (Fig.3). Interestingly, chemogenetic excitation of the neurons in the fastigial nucleus that are projected by the dorsal raphe nucleus also increases stride length, showing a similar pattern (Fig.4).

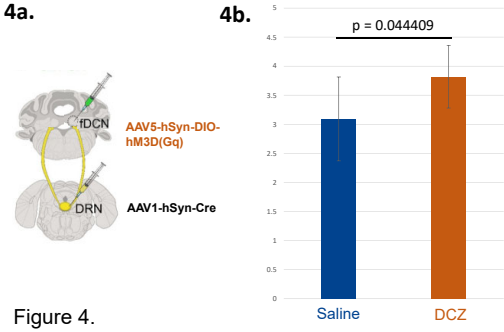

Figure 4.
(a) Scheme for gait analysis of dorsal raphe nucleus excitation tests (b) Stride length of ipsilateral foot to the injected brain.

We reason that this because serotonin from the dorsal raphe might increase activity in the fastigial nucleus via 5-HT_{2A} receptors, which are G_q-coupled receptors. Further, as the serotonergic neurons in the dorsal raphe nucleus are well-known for stress activity, this circuit might be important in regulating movement during stress-related situations to generate appropriate behavioral responses to the environment.

Acknowledgement

K-Brain Project RS-2023-00266872