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Projection from Rostral Ventromedial Medulla to Spinal Trigeminal Nucleus Modulate Masseter Pain

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Introduction

Chronic masticatory muscle pain presents a formidable clinical challenge, and its underlying mechanism remains incompletely elucidated. In prior research, we established a rat model of experimental occlusal interference (EOI) induced masseter hyperalgesia, and demonstrated the involvement of the rostral ventromedial medulla (RVM) in this pathological condition. However, the specific neuronal subtypes within the spinal trigeminal nucleus (Sp5) that receive projections from the RVM, as well as their roles in EOI-induced masseter hyperalgesia, remain uncertain. This study aims to discern the subtype of Sp5 neurons innervated by the RVM, shedding light on the mechanism governing the descending projection from the RVM to the Sp5 and its role in modulating masseter hyperalgesia induced by EOI.

Material and methods

First, we determined the neuronal subtype and the proportion of Sp5 neurons receiving RVM innervation through transsynaptic anterograde tracing. Subsequently, we examined the projection patterns of these Sp5 neurons throughout the entire brain and conducted an analysis of the subtypes of GABAergic Sp5 neurons receiving RVM projections using immunofluorescence staining. Next, we investigated the average proportions of activated GABAergic or glutamatergic Sp5 neurons that received RVM projections in EOI rats. Additionally, we assessed the impact of chemogenetic activation of GABAergic neurons or inhibition of glutamatergic Sp5 neurons, both receiving RVM projections, on the masseter hyperalgesia induced by EOI.

Results

1. Identify the neuronal subtype and proportion of Sp5 neurons that receive RVM projections

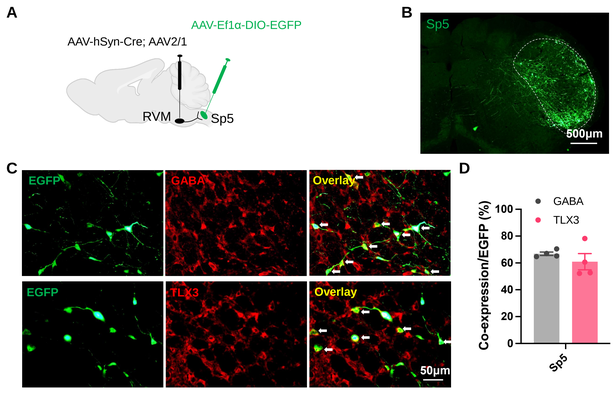
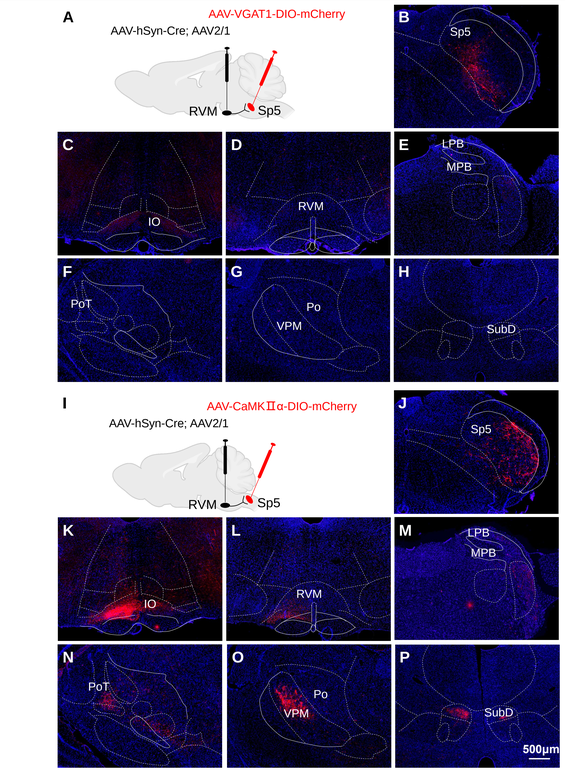


Figure 1. Both GABAergic and glutamatergic Sp5 neurons receive RVM projections.

2. Local and remote projections from Sp5 neurons that receive RVM projections



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	Sp5	IO	RVM	PB	Thalamus			
					PoT	Po	VPM	SubD
GABAergic neurons	+++	-	-	-	-	-	-	-
Glutamatergic neurons	++++	++++	++	+	++	+	++++	+++

Figure 2. The soma and fibers distribution of GABAergic and glutamatergic Sp5 neurons that receive RVM inputs.

3. Identify the neuronal subtype and proportion of GABAergic Sp5 neurons that receive RVM projections

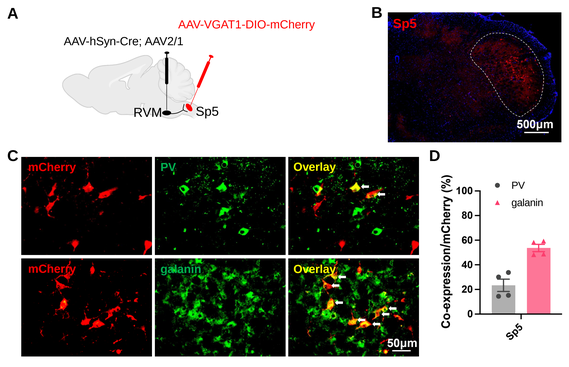

Figure 3. GABAergic Sp5 neurons that receive RVM projections are primarily identified as PV- and galanin-positive interneurons.

4. Activation of both GABAergic and glutamatergic Sp5 neurons receiving RVM inputs in EOI-induced masseter hyperalgesia.

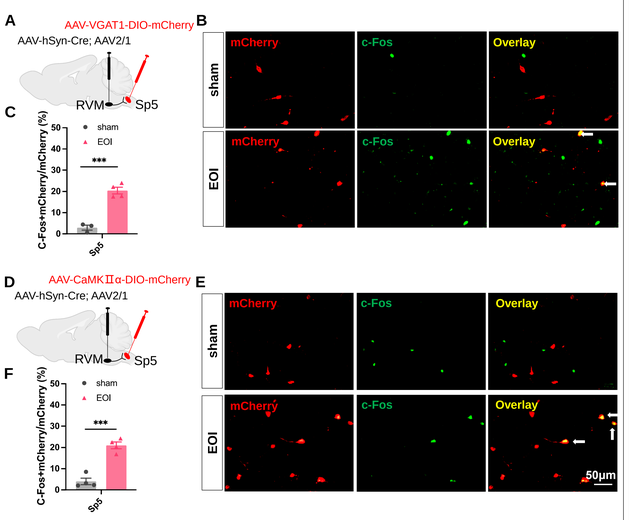

Figure 4. In EOI rats, there was an increase in the number of activated GABAergic and glutamatergic Sp5 neurons receiving RVM inputs. ***, $P < 0.001$.

5. Chemogenetic activation of GABAergic Sp5 neurons or inhibiting glutamatergic Sp5 neurons that receive RVM projections reversed masseter hyperalgesia.

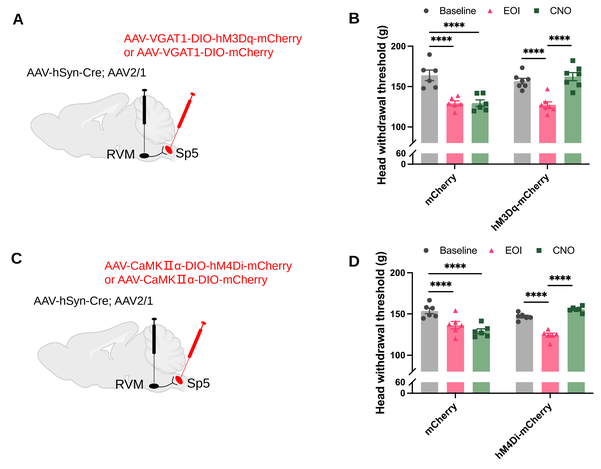

Figure 5. Chemogenetic activation of GABAergic neurons or inhibition of glutamatergic neurons in the Sp5 innervated by RVM resulted in the reversal of EOI-induced masseter hyperalgesia. ****, $P < 0.0001$.

6. Chemogenetic consecutive activation of GABAergic Sp5 neurons receiving RVM inputs blocks the development of EOI-induced masseter hyperalgesia

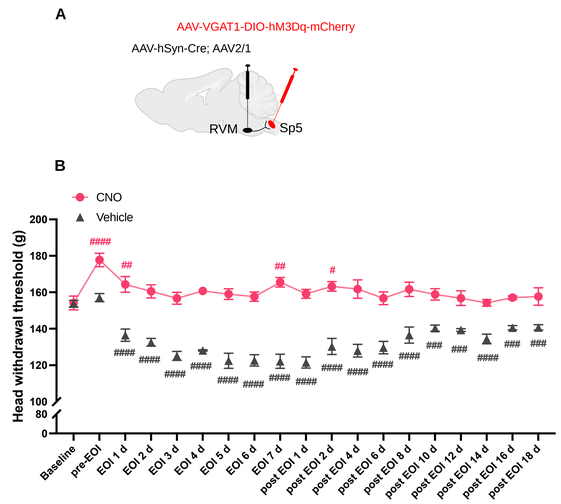

Figure 6. The consecutive activation of GABAergic Sp5 neurons receiving RVM inputs blocks the development of EOI-induced masseter hyperalgesia. #, $P < 0.05$; ##, $P < 0.01$; ###, $P < 0.001$; ####, $P < 0.0001$.

Conclusion

In conclusion, our study delineates the specific cell types of Sp5 neurons that receive projections from the RVM. The dysregulation of endogenous descending facilitation and inhibition originating from the RVM plays a crucial role in the development of EOI-induced masseter hyperalgesia. These findings enhance our current comprehension of the neural mechanisms governing the endogenous descending pain modulation system, particularly its bidirectional impact on masticatory muscle pain.

Acknowledgements

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Ethical Permissions

The study was approved by the Institutional Animal Care and Use Committee of Peking University.