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Macromolecular assembly of nitrergic neurotransmission in gastric smooth muscle nerve terminals

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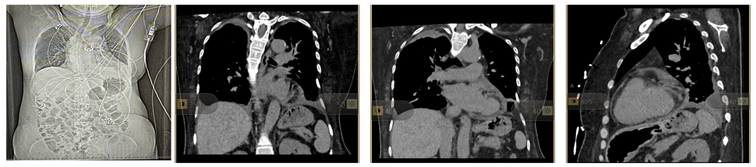
Pathophysiology of functional bowel disorders are elusive

Severe *retrosternal chest pain in Bethlem myopathy*

57-year-old female from Nepal presented with severe retrosternal chest discomfort for 1d. Troponins negative; saturating appropriately on room air. Nonsmoker, complained of poor oral intake for the last few days. Though her appetite was intact, she took only small portions of food. There were no concerns for melena or bright red blood per-rectum. She also denied any chest discomfort related to her meals. Unfortunately, she has been wheelchair-bound for the last several years. Neurological examination showed mild weakness in her upper & lower extremities but no contractures. Biopsy of the right quadriceps muscle showed atrophic myopathic myocytes with fibrosis. Extensive sarcolemmal alpha sarcoglycan, beta sarcolycan, delta sarcoglycan, & dysfarlin were observed. Gamma sarcoglycan immunoreactivity was observed in most of the fibers. This is concerning for limb girdle muscular dystrophy 2c. Clinical exome sequence analysis was performed (Xome Dx), which showed heterozygous for a pathogenic variant in the COL6A1 gene (c806G>A, G269E, autosomal dominant). This is diagnostic of Bethlem myopathy.



Introduction

Unlike skeletal neuromuscular junctions & asymmetric Gray synapses in CNS, intervals between motor nerve terminals & smooth muscles in the gastrointestinal tract has no specialized structure. Particularly, there is no visualized active zone [1,2].

However, neuronal nitric oxide synthase (nNOS), the major synthesizer of inhibitory neurotransmitter nitric oxide (NO), docks at the nerve terminal membranes with the aid of assembly proteins like postsynaptic density protein 95 (PSD95), shank & potentially proteins like gephyrin [1,3,4].

Aim of Study

To examine the definitive role of PSD95 in nitrergic neurotransmission

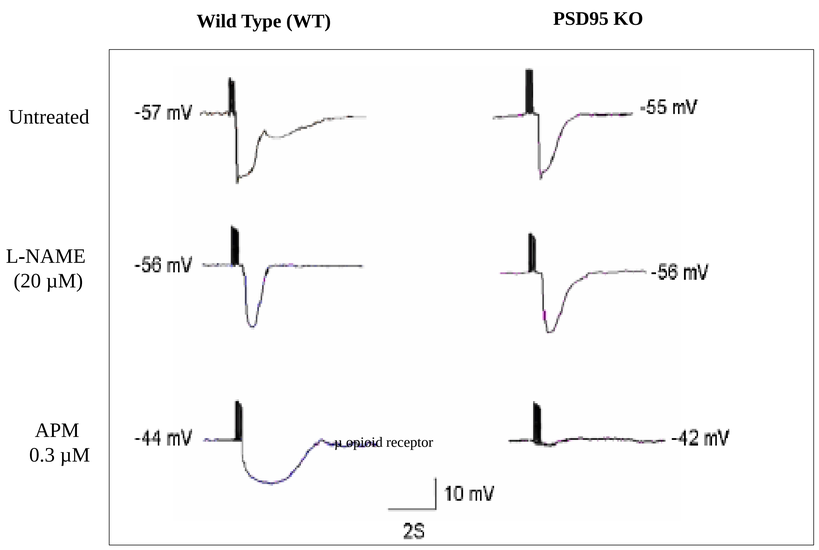
Materials & Methods

Male C57BL/6J mice (4–6 wks) & PSD95 knockout (n=4, respectively)[5].

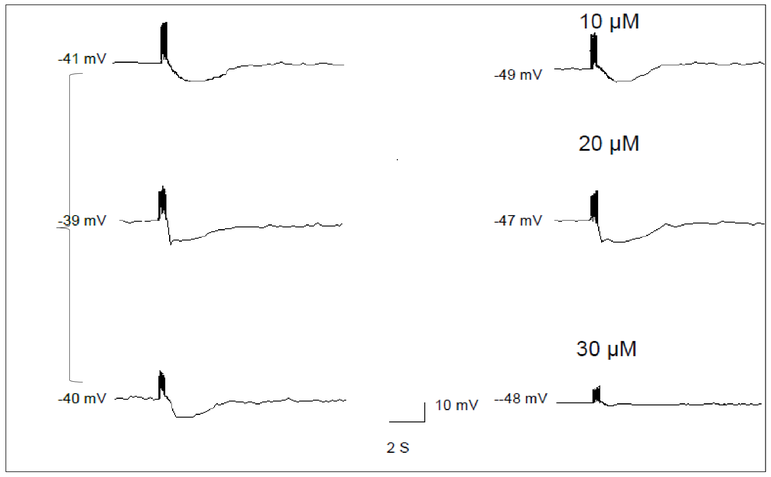
Intracellular electrophysiological techniques were implemented to measure the inhibitory junction potentials (IJPs) from the gastric

Results

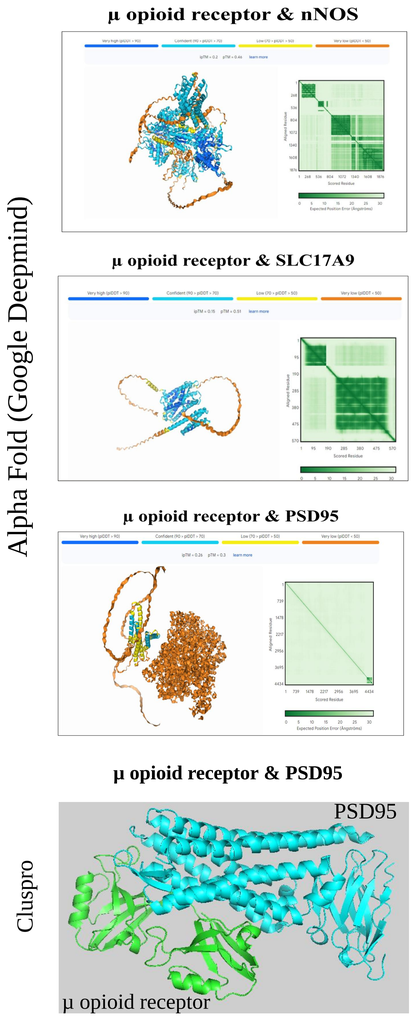
Loss of nitrergic (slow) IJP in PSD95 KO



Loss of purinergic (fast) IJP & nitrergic (slow) IJP with 2-bromopalmitate treatment



Protein interactions of nNOS apparati with µ opioid receptor



Summary & Conclusion

Our study demonstrates that PSD95 facilitates the assembly of macromolecular complexes for nitrergic neurotransmission.

nNOS & µ opioid receptor may interact

Achalasia is seen in COL19 mutation[6]. Our patient with COL6 mutation showed diffuse motility problems. Gain of function mutation of col6A has been reported in Down syndrome & Hirschsprung disease[7].

The exact role of interjunctional collagens in nitrergic neurotransmission is unclear

Reference

(1) Chaudhury 2014 (2) Goyal and Chaudhury 2013 (3) Chaudhury *et al.*, 2009 (4) McMahan *et al.*, 2024 (5) Migaud *et al.*, 1998 (6) Sumiyoshi *et al.*, 2004 (7) Soret *et al.*, 2015.

The authors wish to thank Xue-Dao He (HMS), Wei-Dong Yao (New England Primate Research Center), Seth Grant (Sanger Institute) & funding agencies.