Disentangling the many roles of D-serine/NMDA receptor system in the enteric nervous system in health and disease

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While the functions of the N-methyl D-aspartate receptors (NMDARs) in the brain have been extensively studied, their roles in the enteric nervous system (ENS) remain paradoxically poorly defined and highly controversial. In addition, emblematic studies during the last two decades have demonstrated that D-amino acids are produced by mammals to support important functions. In particular, D-serine has gained traction as a key signaling molecule for synaptic circuits and memory encoding by binding to NMDARs. Despite important progress, whether D-serine and more generally D-amino acids could be produced in the mammalian gut by the host cells and if it could regulate the activity of the ENS and gastrointestinal (GI) functions has remained unexplored. Here, we uncover a new role for D-serine and non-conventional GluN1-GluN3 NMDARs in regulating ENS functions. We demonstrate that d-Ser is produced by serine racemase (SR) expressed in enteric neurons. By using both in situ patch clamp recording and calcium imaging, we show that D-serine alone acts as an excitatory neurotransmitter in the ENS independently of the conventional GluN1-GluN2 NMDARs. Instead, D-serine directly gates the non-conventional GluN1-GluN3 NMDARs in enteric neurons from both mouse and guinea-pig. Pharmacological inhibition or potentiation of GluN1-GluN3 NMDARs had opposite effects on mouse colonic motor activities, while genetically driven loss of SR impairs gut transit and fluid content of pellet output. Our results demonstrate the existence of native GluN1-GluN3 NMDARs in enteric neurons and open new perspectives on the exploration of excitatory D-serine receptors in gut function and diseases.