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**Background:** MeCP2, the gene mutated in Rett syndrome (RTT) is involved in synaptic plasticity. Recent clinical reports disclose that Rett patients suffer from gastrointestinal (GI) dysmotility. We hypothesize that this could be due to impaired synaptic function in the enteric nervous system (ENS).

**Objectives:** Provide evidence of the presence of MeCP2 in the ENS and explore how it mediates proper GI motility.

**Methods:** In vivo studies were carried out to determine whether MeCP2 KO mice reproduced the GI dysmotility seen in RTT. Immunohistochemical studies were carried out to examine the status of MeCP2 in GI tissue. To provide evidence for ENS homeostatic plasticity and its dysfunction in RTT, we performed plasticity experiments on dissociated enteric neurons and investigated neurotransmitter imbalances in MeCP2-KO GI tissue by western blot.

**Results:** MeCP2 KO mice reproduced the GI dysmotility seen in RTT. Human and murine GI tissue displayed prominent nuclear labelling using an antibody to MeCP2 only in neurons. The exclusivity of MeCP2's presence implies neuronal dysfunction likely mediates the GI pathology. MeCP2 KO GI tissue demonstrated increased levels of inhibitory neurotransmission markers. As well, neuronal nitric oxide synthase, which synthesizes the inhibitory neurotransmitter nitric oxide, is increased following moderate, prolonged stimulation by hyperkalemia.

**Conclusions:** MeCP2 plays an important role in proper GI motility. Neurotransmitter imbalances likely mediate the GI pathology seen in RTT. These imbalances may be due to dysfunction in homeostatic plasticity mechanisms.