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Rett syndrome (RTT) is a neurological disorder caused by the X-linked MECP2 gene mutation. Previously, we demonstrated that the Huntingtin-dependant (Htt) axonal transport is altered when Mecp2 is lacking, partly due to a deficit of the molecular motor contents (Roux et al., 2012). However, the neuronal trafficking is also strongly dependent on the phosphorylation level of Htt at serine 421 (S421). Therefore, we developed several tools in order to stimulate pharmacologically Htt phosphorylation at S421 in vivo and in vitro using: 1) a direct activation of the Akt pathway, through the stimulation of the insulin/IGF1 receptors or, 2) the indirect blocking of the Htt dephosphorylation using Fk506. Thereafter, we used a genetic approach by crossing Mecp2 deficient mice with knock in mice expressing either an aspartic acid or alanine at position 421 to mimic tonic phosphorylation (S421D) or to prevent phosphorylation (S421A), respectively. For both pharmacology and genetic crossing we used a battery of behavioral tests in order to evaluate the in vivo consequence: grip strength, rotarod, open field and the respiratory profile during postnatal development are performed. Altogether our results indicate that modulation of Htt at serine 421 is a promising way to improve the neuronal trafficking in RTT and a possible target to develop treatments.