Chronic rapamycin administration after high-thoracic spinal cord injury exacerbates cardiovascular dysfunction

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Background: The mammalian target of rapamycin (mTOR) is a master regulator of protein synthesis that coordinates critical functions such as cell growth and metabolism. Experimental evidence shows that targeted enhancement of mTOR activity after spinal cord injury (SCI) promotes robust axonal sprouting and functional recovery. However, we have shown that the development of 'autonomic dysreflexia' (AD) after high-thoracic SCI, manifested as episodic hypertension in response to noxious visceral stimulation below the injury level, correlates temporally with maladaptive plasticity of viscero-sympathetic reflex pathways.

Purpose: Test the hypothesis that inhibition of mTOR using the FDA-approved immunosuppressive drug rapamycin (RAP) can suppress aberrant sprouting and attenuate the development of AD, as measured by telemetric hemodynamic monitoring.

Methods: Adult female Wistar rats were implanted with telemetry probes into the descending aorta to continuously record blood pressure and heart rate for the duration of this study. One week later, rats received complete spinal cord transection at the fourth thoracic level. Beginning immediately after SCI, animals were treated with rapamycin (3 mg/kg i.p., 1x every other day) or vehicle for 4- weeks. AD was induced weekly starting at week 2 using noxious colorectal distension (CRD). Spontaneously occurring AD (sAD) was automatically detected throughout the study and quantified using our published algorithm. Following terminal CRD at 4-weeks post-injury, spinal cords were collected and processed for either western blot analyses or ongoing histological analysis of primary afferent sprouting to be correlated with quantified hemodynamic outcome measures.

Results: Chronic RAP treatment suppressed mTOR activity in the spinal cord as measured by reduced phosphorylation of the downstream ribosomal protein S6. RAP had substantial adverse effects on body weight and hemodynamic parameters, particularly after injury. SCI-induced weight loss was exacerbated by RAP, which also prevented return to pre-injury weights by 4 weeks. Moreover, SCI rats receiving RAP had significantly higher daily mean arterial pressure (MAP) and heart rate (HR) compared to vehicle treatment throughout the study. Comparatively, naïve rats receiving RAP showed slightly elevated daily MAP and decreased HR versus vehicle controls. Importantly, whereas the daily frequency of sAD episodes was significantly increased by RAP treatment after SCI, the magnitude of CRD-induced AD was not different at any time-point assessed.

Conclusions: Chronic RAP treatment has adverse effects on body weight recovery and already compromised cardiovascular function after SCI. Ongoing analyses are investigating whether or not these effects correspond to maladaptive changes in viscero-sensory-sympathetic circuitry.

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