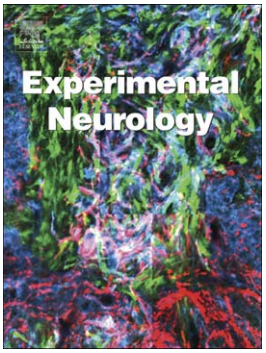

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Combinatorial Influences of Paclitaxel and Strain on Axonal Transport

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Abstract: Paclitaxel is an effective chemotherapeutic that, despite its common use, often causes peripheral sensory neuropathy. In neurons, paclitaxel binds to and stabilizes microtubules, and through unknown mechanisms, bundles microtubules and disrupts their organization. Because microtubules serve as tracks on which a variety of axonal cargoes are transported, a leading hypothesis for the etiology of paclitaxel-induced neuropathy is that these changes to microtubule organization impair axonal transport. In addition to supporting transport, microtubules also serve a structural role, accommodating axonal extension occurring during axonal growth or joint movement. In light of this dual role for microtubules, we tested the hypothesis that axonal stretch amplified the effects of paclitaxel on axonal transport. Embryonic rat dorsal root ganglia were cultured on stretchable silicone substrates, and parameters describing the axonal transport of three distinct cargoes – mitochondria, synaptophysin, and actin – were measured with and without paclitaxel treatment and axonal strain. Paclitaxel treatment, particularly in combination with stretch, led to severe perturbations in a number of transport parameters, including the number, velocity, and travel distance of cargoes in the axon. Our results suggest that mechanical loading of neurons can exacerbate transport deficits associated with paclitaxel treatment, raising the interesting possibility that paclitaxel influences neuronal function in a multi-factorial manner.