A Caudal Twist in the Tale: The Spinal Cord and Dystonia

Comment on: Pathophysiology of Dyt1-Tor1a dystonia in mice is mediated by spinal neural circuit dysfunction Pocratsky AM, Nascimento F, Özyurt MG, White IJ, Sullivan R, O'Callaghan BJ, Smith CC, Surana S, Beato M, Brownstone RM. Sci Transl Med. 2023 May 3;15(694): eadg3904. doi: 10.1126/scitranslmed.adg3904[1]

A recent study by Pocratsky et al.[1] has blown open a debate on whether the spinal cord has been a blind spot in dystonia research. Their starting point was DYT-*TOR1A* dystonia, engineering a mouse model with site specificity so that *Tor1a*-torsinA was expressed in the brain, but not the spinal cord and dorsal root ganglia. The spectrum of motor signs exhibited by the mouse mutant were strikingly similar to humans with manifesting DYT-*TOR1A*: early onset hindlimb postural abnormalities that preceded debilitating and progressive pelvis, trunk, and forelimb torsion. This was particularly notable as previous rodent models manipulating *Tor1a* in the cortex, basal forebrain, basal ganglia, or cerebellum have not exhibited such a convincing repetition of the human phenotype. Experimental evidence for dysfunctional spinal circuits in dystonia was then built. Screening for ultrastructural signatures found that ~60% of spinal neurons had findings classical for torsinA loss. Neurophysiological tests also revealed features consistent with those noted in humans, with spontaneous and excessive muscular activity at rest and multiple bouts of co-contractions between agonist–antagonist muscles during movements.

Pocratsky's work, therefore, opens core and fundamental questions about the origins of dystonia. We have known since the 1980s that reciprocal inhibition between opposing muscles is reduced in the spinal cord.[2] However, the abnormalities found were assumed to be related to defective descending control on spinal cord and the curiosity moved to higher-order areas. These assumptions are now challenged and the discussion of the role of spinal cord circuits within dystonic neural networks is wide open. Overall, it remains unlikely that spinal cord acts as an isolated agent in the production of dystonia. Most simply, the spinal cord alone cannot generate sustained movement as evidenced by the paralysis of spinal segments below sites of injury, despite functional local spinal circuits. However, in dystonia, there remains the possibility that corruption of movement appears downstream from the brain. If the spinal cord is the dominant causal site, this is still likely to lead to altered central nervous system connectivity, which could influence the phenotype. One goal for future empirical work is, therefore, to establish the developmental order of pathophysiological changes, which changes are primary drivers, and which occur in response to the primary event.

Generalization of these findings to human DYT-*TOR1A* dystonia should be tentative. The reported knockout was a biallelic *Tor1a* knockout (with 100% penetrance) and human DYT-*TOR1A* dystonia is because of a mutation in a single allele (penetrance of ~30%). Inherited biallelic variants in humans leads to *TOR1A*-associated arthrogryposis multiplex congenita 5 that presents prenatally or in early childhood with a severe and complex phenotype (flexion contractures, developmental delay, mixed motor symptoms, dysmorphic features, and neuroradiological features).[3] Furthermore, this animal model relates specifically to DYT-*TOR1A* dystonia, the relative causal contribution of the spinal circuitry across subtypes of dystonia remains to be determined.

However, in defense of this clever work by Rob Brownstone's team, there is a full house of classical dystonia findings across multiple levels of description. As noted in their conclusion, their work firmly places the spinal cord within the dystonia circuitopathy, and the hope is that this may open new treatment strategies that target pathophysiology resident in the spinal cord. ■

Data Availability Statement

NA

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