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Stressing the Importance of Cholinergic Interneurons in Striatal Function

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When pathological stressors threaten cellular health and function, the integrated stress response (ISR) may be recruited as a rescue response. An evolutionarily conserved signaling pathway, the ISR broadly dampens protein synthesis while also triggering translation of select transcription factors, effectively serving as a translational reset button once stressors have set the proteome into disequilibrium[1]. Perhaps not surprisingly, activation of the ISR occurs in a variety of neuropathologies, including movement disorders such as dystonia[2].

Writing in *Science*, Helseth, Hernandez-Martinez and colleagues have now identified a surprising new role for constitutive ISR signaling in the normal physiology and function of striatal cholinergic interneurons (CINs)[3]. The team developed a genetically-encoded biosensor, termed “SPOTlight”, that could be used to identify cells with active ISR signaling. SPOTlight reports ISR signaling by means of two fluorophores which are expressed with mutual exclusivity depending upon the phosphorylation status of eukaryotic initiation factor 2 alpha (eIF2α). Because phosphorylation of eIF2α is an integral component of the ISR, relative expression of the two SPOTlight fluorophores reports the ISR signaling state on a single-cell level. When SPOTlight was expressed in the brains of mice, ISR-labeled neurons were sparsely distributed across heterogenous regions and cell types, suggesting stochastic, low-level ISR induction in the healthy brain. An exception was discovered in the striatum, where CINs were uniformly strongly labeled by the ISR sensor. This unexpected finding raised the possibility that constitutive ISR signaling contributes to normal CIN function. Although they are a rare cell type in striatum, CINs play pivotal roles in the striatal microcircuitry, in part due to their powerful and reciprocal interactions with the mesostriatal dopamine system[4]. CINs express the D2 dopamine receptor (D2R), and application of D2R agonists normally lowers spontaneous CIN firing rates. However, when the authors inhibited ISR signaling, using either pharmacologic or genetic approaches, the latter selectively in CINs, a D2R agonist increased CIN firing. Activation of CINs can drive striatal dopamine release through cholinergic receptors located on striatal dopaminergic terminals. Consistently, disruption of CIN ISR signaling resulted in an amplification, rather than blunting, of striatal extracellular dopamine levels by a D2R agonist. Lastly, the authors tied these findings together in demonstrating that performance of a learned motor skill, a process in which striatal CIN-dopamine interactions may be intimately involved, is invigorated by inhibition of CIN ISR signaling.

Competing Interests: None

These new results highlight a critical role for the ISR in normal CIN function, and raise important questions regarding the mechanism(s) by which the ISR regulates D2R signaling within CINs, and possibly other signaling cascades used by these cells. Additional new questions concern the possibility of regional variability of CIN ISR function across the striatum[5], as well as the potential disruption of this signaling in various neurological disease contexts, including movement disorders[4].

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