Autism and "Astro"logy: New insights from recordings in human brain cells

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Important insights into the pathophysiology of Fragile X Syndrome (FXS), a common monogenic cause of autism spectrum disorder, have emerged from analyses of rodent models. However, these findings have been less effective in developing therapeutic interventions, thereby highlighting the need for model systems of human origin. Moreover, earlier studies focused on neurons, and the role of glia remains largely unexplored in FXS. Here, we used human induced pluripotent stem cells to examine the potential role of astrocytes in physiological abnormalities in FXS neurons. Whole-cell recordings from FXS cortical neurons, co-cultured with FXS astrocytes, revealed spontaneous bursts of action potentials that are more frequent, but shorter in duration, compared to control neurons co-cultured with control astrocytes. However, the same FXS neurons, when co-cultured with control astrocytes, fire like controls. Conversely, control neurons exhibit aberrant firing in the presence of FXS astrocytes. Thus, the genotype of astrocytes determines the physiological phenotype of neurons. Strikingly, even astrocytic conditioned medium by itself is capable of eliciting the same effects. Next we examined the mechanisms through which the astrocytic secretome mediates these effects in neurons. We found higher levels of the astroglial-derived protein, S100b, in FXS astrocytes and its conditioned medium. And high levels of S100b, in turn, trigger aberrant neuronal firing. A lower level of S100b, in contrast, restores normal firing by reversing the suppression of a persistent sodium current in FXS neurons. Together, these results reveal an important non-cell-autonomous contribution of astrocytes in correcting aberrant electrical activity in human FXS neurons, thereby suggesting a framework for exploring new therapeutic strategies aimed at neuron-glia interactions.

Invited by Ron Stoop
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