Examining the Role of Transcription Factors, Nr4a1, Foxp1, and Olig2, in the Development of Medium Spiny Neurons from the Q175 Mouse Model of Huntington's Disease

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Huntington’s disease (HD) is a fatal, autosomal dominant, neurodegenerative disease that currently has no cure. Most neurodegeneration occurs in the striatum, which is comprised of 95% medium spiny neurons (MSNs) and has two compartments: the striosomes and matrix. This study aimed to determine if specific transcription factors – Nr4a1, Foxp1, and Olig2 – and/or brain derived neurotrophic factor (BDNF) could help protect MSNs in the striatum. The study was two-fold and utilized the q175 mouse model, a knock-in model of HD. First, MSN development in the presence of the different transcription factors was analyzed by comparing the levels of DARPP-32, an established marker for healthy MSNs, in q175 and in WT primary cell cultures. Next, through qPCR analysis, the striosomes and matrix were examined by determining the levels of their specific markers (MOR1 and Calbindin respectively) to elucidate the impact each transcription factor has on these structures. Results showed that each transcription factor was able to prevent the dramatic decrease in DARPP-32 in q175 MSNs ($p<0.05$ qPCR and $p<0.0001$ immunocytochemistry). Moreover, Nr4a1 and Olig2 increased the levels of MOR1 mRNA in the q175 primary cell cultures ($p<0.01$). Overall, this study determined that Nr4a1, Foxp1, and Olig2 aided the development of q175 MSNs. Specifically, we provide novel findings regarding the role of Nr4a1 and Olig2, transcription factors which have not been studied relative to MSN development or in HD. Additionally, we have begun to clarify the distinct role these transcription factors have on the compartments of the striatum, which have yet to be explored in the literature. With this knowledge as a foundation, further development of a therapeutic approach could have a profound impact on HD patients.

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