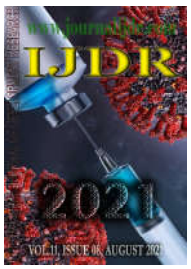
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 08, pp. 49394-49395, August, 2021
https://doi.org/10.37118/ijdr.22593.08.2021



RESEARCH ARTICLE OPEN ACCESS

NU-9 AND AMYOTROPHIC LATERAL SCLEROSIS: IMPROVING MITOCHONDRIA AND ENDOPLASMIC RETICULUM STABILITY?

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Article History: Received 26th May, 2021; Received in revised form 17th June, 2021; Accepted 11th July, 2021; Published online 26th August, 2021.

Citation: **Marco Orsini; Marcos RG de Freitas; Acary Bulle Oliveira; Carlos Henrique Melo Reis; Valéria Camargo Siveira; Adriana Leico Oda; Cristina Salviori; Antônio Marcos da Sila Catharino; Maurcio Sant' Anna Junior and Carlos Eduardo Cardoso. 2021.** "Nu-9 and amyotrophic lateral sclerosis: improving mitochondria and endoplasmic reticulum stability?", *International Journal of Development Research*, 11, (08), 49394-49395.

INTRODUCTION

In order to mimic the process of deterioration of motor neurons, numerous studies have conducted research to better understand the pathophysiology of Amyotrophic Lateral Sclerosis (ALS), which is a progressive, degenerative and inexorable disease. It is from the processes involved in the genesis of the disease that strategies can be created to block or delay the process of programmed cell death. The development of an experimental model that mimics the sporadic or genetic context of ALS serves to test new drugs[1]. In this context, NU-9 administration, a compound initially identified based on its ability to reduce mSOD1 toxicity, has profound impact on improving the health and stability of UMNs, as identified by detailed cellular and ultrastructural analyses[1-2]. The administration of NU-9 in animal models improved the structure of mitochondria and the rough endoplasmic reticulum, due to reduced levels of misfolded superoxide dismutase (mSOD1) protein. In these studies, there was a stabilization of the apical dendrites in degenerating upper motor neurons and, consequently, a positive interference in the motor behavior measured by the suspended wire test. A slowdown in the continuous process of degeneration of neurons that make up the pyramidal tract was observed in cases of mSOD1 and TDP-43 pathology models, two broad, specific and distinct causes of ALS, important for motor neuron degeneration[2-4]. Since each of these mutations are identified on genes that code for a protein, and because cellular functions mostly depend on protein-protein interactions, we hypothesized that the mutations detected in patients and the alterations in protein interaction domains would hold the key to unravel the underlying causes of their vulnerability. Betz cells (located within the fifth layer of gray matter in the primary motor cortex) of patients with TDP-43 pathology display a distinct set of intracellular defects especially at the site of nuclear membrane, mitochondria and endoplasmic reticulum (ER). Numerous TDP-43 mouse models have been generated to discern the cellular and molecular basis of the disease, but mechanisms of neuronal vulnerability remain Unknown.

The administration of NU-9 serves as a bridge for this process, stabilizing the mitochondria and providing the endoplasmic reticulum (a region that has a continuous membrane to the outer membrane that surrounds the nucleus) with adequate storage of proteins used by cells or exported to various sites of acting; among them the structures and neuronal signaling pathways of the central nervous system[5]. Corticospinal motor neurons (CSMN) vulnerability is marked by selective degeneration of apical dendrites especially in layer II/III of the hSOD1(G93A) mouse motor cortex, where cortical input to CSMN function is vastly modulated. Although studies have already identified the presence of large amounts of astrocytes and microglia in this process of involvement of the first motor neuron, these are undoubtedly not the beginning markers for the process of cell death. There are defects in cortical modulation, considered to be supposed targets as a potential cause of neuronal vulnerability in patients with Amyotrophic Lateral Sclerosis; mainly after molecular findings marked in SOD1 and TDP43 models. The use of NU-9 seems to have the function of preceding this entire process and avoiding an abnormal signaling cascade, preserving primordial cells for the viability of superior motor control mechanisms[6]. It remains unclear whether widely accepted transgenic ALS models, in particular hSOD1(G93A) mice, undergo degeneration of CSMN and molecularly/developmentally closely related populations of nonmotor projection neurons [e.g., other subcerebral projection neurons (SCPN)], and whether potential CSMN/SCPN degeneration is specific and early. Microglial activation (cells that inspect the local microenvironment and respond to injury by releasing pro-inflammatory molecules and phagocytic clearance of apoptotic cells) in ALS can be protective or degenerative for neurons. Among others, mutations in superoxide dismutase 1 (SOD1), chromosome 9 open reading frame 72 (C9Orf72), transactive response DNA-binding protein (TDP) 43, and vacuolar classification-associated protein 54 (VPS54) genes have been associated with ALS. A dual role and functionality of microglia in four different in vivo ALS models and the search for a common denominator regarding the role of microglia

in ALS have already been described; who can behave like a villain or be beneficial[7]. We believe that NU-9 also has an indirect role in the modulation of microglial cells; either through the mediation of neighboring cells that make connections, or through obscure signaling mechanisms of the central nervous system that are still unknown. NU-9 appears to modulate them in order to preserve the higher motor neurons. NU-9, a compound that was previously characterized toreduce mSOD1 aggregates in cell lines and a compoundthat crosses the blood brain barrier with favorable pharmacokinetic properties, has the unique ability to improvethe structure and the integrity of both mitochondria andER. This unique ability results in enhancing the cytoarchitectural integrity of degenerating UMNs and, most importantly, stopping the progressive degeneration of UMNs thatbecome diseased as a result of mSOD1 toxicity and TDP-43 pathology, two independent and overarching causes ofneurodegeneration. NU-9 treatment also increased the average numberof intact ER cisternae in UMNs that become diseasedas a result of TDP-43 pathology[8].

REFERENCES

McColgan P, Joubert J, Tabrizi SJ, Rees G. The human motorcortex microcircuit: insights for neurodegenerative disease. NatRevNeurosci. 2020 (21);(8): 401-415.

Genç B, Gautam M, Gözütok Ö, Dervishi I, Sanchez S, Goshu GM, Koçak N, Xie E, Silverman RB, Özdinler PH. Improving mitochondria and ER stability helps eliminate upper motor neuron degeneration that occurs due to mSOD1 toxicity and TDP-43 pathology. ClinTransl Med. 2021 Feb;11(2):e336. doi: 10.1002/ctm2.336. PMID: 33634973; PMCID: PMC7898037.

Brunet A, Stuart-Lopez G, Burg T, Scekic-Zahirovic J, RouauxC. Cortical circuit dysfunction as a potential driver of amyotrophic lateral sclerosis. Front Neurosci. 2020;14. 363.

Gozutok O, Helmold BR, Ozdinler PH. Mutations and Protein Interaction Landscape Reveal Key Cellular Events Perturbed in Upper Motor Neurons with HSP and PLS. Brain Sci. 2021 Apr 29;11(5):578. doi: 10.3390/brainsci11050578. PMID: 33947096; PMCID: PMC8146506.

Gautam M, Jara JH, Kocak N, Rylaarsdam LE, Kim KD, Bigio EH, HandeÖzdinler P. Mitochondria, ER, and nuclear membrane defects reveal early mechanisms for upper motor neuron vulnerability with respect to TDP-43 pathology. Acta Neuropathol. 2019 Jan;137(1):47-69. doi: 10.1007/s00401-018-1934-8. Epub 2018 Nov 19. PMID: 30450515; PMCID: PMC6339587.

Jara JH, Villa SR, Khan NA, Bohn MC, Ozdinler PH. AAV2 mediated retrograde transduction of corticospinal motor neurons reveals initial and selective apical dendrite degeneration in ALS. Neurobiol Dis. 2012 Aug;47(2):174-83. doi: 10.1016/j.nbd.2012.03.036. Epub 2012 Apr 11. PMID: 22521461; PMCID: PMC4049520.

Cihankaya H, Theiss C, Matschke V. Little Helpers or Mean Rogue-Role of Microglia in Animal Models of Amyotrophic Lateral Sclerosis. Int J Mol Sci. 2021 Jan 20;22(3):993. doi: 10.3390/ijms22030993. PMID: 33498186; PMCID: PMC7863915.

Gautam M, Xie EF, Kocak N, Ozdinler PH. Mitoautophagy: aunique self-destructive path mitochondria of upper motor neu-rons with TDP-43 pathology take, very early in ALS. Front CellNeurosci.2019;13;489.

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