Research project

Title

"A potential metabolic-targeted therapeutic for Amyotrophic lateral sclerosis (ALS): Leptin"

Description

Amyotrophic lateral sclerosis (ALS), a devastating neurodegenerative disease, has no effective treatment. There is a great need to improve upon current therapeutic approaches for ALS. A growing body of evidence highlights the relationship between lifestyle risk factors related to metabolism and ALS. Indeed, being **obese confers a survival advantage in ALS and is associated with a reduced risk of developing ALS**.

Accordingly, it has been found that leptin, a hormone produced by adipocytes, is strongly related to ALS risk. However, no study **has determined whether** leptin could have an effect *per se* besides being correlated with fat mass in ALS.

Importantly, **leptin is a neuroendocrine modulator of the immune system,** and the potential role of inflammation in ALS is gaining attention because systemic low-grade inflammation is associated with dysfunctional metabolic homeostasis in ALS. However, the functional effects of leptin in the pathophysiology of inflammation associated with dysfunctional metabolic homeostasis in ALS, remains unexplored.

Interestingly, metabolic changes are also observed in patients with frontotemporal dementia (FTD), which exists on a continuous clinical spectrum with ALS. Significantly, most cases of ALS and 50% of FTD cases are characterized by pathological disturbances in TAR DNA-binding protein of 43 kDa (TDP-43). Furthermore, it has been reported that leptin and TDP-43 are linked in ALS.

The main objective of this project is to address if inducing leptin resistance, through dietary manipulation, could ***reduce the bioenergetic stress in ALS.*** To achieve this, we will use several complementary *in vivo* and *in vitro* TDP-43 tools: a transgenic mouse model of ALS, which expresses mutant human TDP-43, a newly described physiological TDP-43 knock-in mouse model of FTD, and human ALS tissues. Our results promise to give us an opportunity to halt the progression of ALS through dietary manipulation or lifestyle changes.

Funding: Fundación Luzón, Fundación "la Caixa"

01/09/2019 – 01/09/2022

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