Development of C75-CoA-loaded polymeric nanomedicines to inhibit CPT1 in specific brain cells

Jesús García-Chica[1,2,3]
West Kristian D. Paraíso[4], Xavier Ariza[3], Jordi García[3], Laura Herrero[2], Núria Casals[1], Dolors Serra[2], Sabina Quader[4], Rosalía Rodríguez-Rodríguez[1].
[1]*Department of Basic Sciences, Faculty of Medicine & Health Sciences, Universitat Internacional de Catalunya, 08195, Sant Cugat del Vallès, Spain.* `
[2]*Department of Biochemistry & Physiology, School of Pharmacy & Food Sciences, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, E-08028, Barcelona, Spain.*
[3]*Department of Inorganic & Organic Chemistry, Faculty of Chemistry, Institut de Biomedicina de la Universitat de Barcelona (IBUB),Universitat de Barcelona, E-08028, Barcelona, Spain*
[4]*Innovation Center of Nanomedicine,Kawasaki Institute of Industrial Promotion, Kawasaki, Kanagawa, 210-0821, Japan.*

Contact email: jgarciac@uic.es

Carnitine palmitoyl transferases are a family of proteins involved in the metabolism of fatty acids. CPT1A in the mitochondria catalyses the conversion of long-chain fatty acids into acylcarnitines. It is expressed in peripheral tissues but also in the hypothalamus, where it is involved in energy homeostasis. Inhibition of hypothalamic CPT1A reduces feeding, whereas overexpression increases food intake and adiposity. Furthermore, CPT1A and CPT1C are overexpressed in glioblastoma, and CPT1C is upregulated in glucose depletion and hypoxia, suggesting a protecting role under these conditions [1,2]. Pharmacological manipulation of CPT1 proteins activity in specific brain cells could therefore be useful in treating diseases such as obesity or glioblastoma.
C75 is a racemic lactone originally described to inhibit FASN. Later it was described that (+)-C75 inhibits CPT1A, while the physiologically formed adduct (-)-C75-CoA inhibits FASN [3,4]. However, peripheral inhibition of CPT1A leads to undesired side effects. To overcome this problem, we have developed a strategy involving polymeric nanoparticles targeted to hypothalamic neurons or glioblastoma cells [5]. We have prepared PEG-PLL nanoparticles which can encapsulate racemic C75 and its enantiopure forms, and can be modified with ligands designed to overcome the blood-brain-barrier and target hypothalamic neurons and glioblastoma cells.

REFERENCES

[1] Sierra AY, Gratacós E, Carrasco P, et al. Journal of Biological Chemistry. 11(2008) 6878-6885.
[2] Casals N, Zammit V, Herrero L, Fadó R, Rodríguez-Rodríguez R, Serra D. . Progress in Lipid Research. 61(2016)134-148.
[3] Mera P, Bentebibel A, López-Viñas E, et al. Biochemical Pharmacology. 6(2009)1084-1095.
[4] Makowski K. PhD Thesis (2012)
[5] Quader S, Liu X, Chen Y, et al. Journal of Controlled Release. 258(2017)56-66.

FIGURES

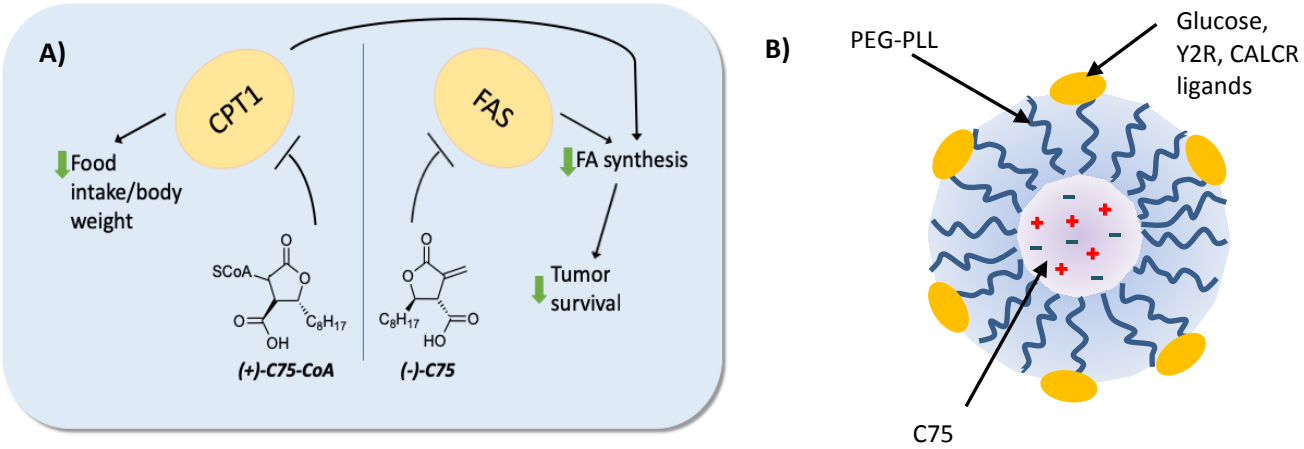

Figure 1: A) C75 action summary. B) Nanoparticle model