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Abstract

A New Nanomedicine Platform to Deliver a Carnitine Palmitoyl-Transferase 1 (CPT1) Inhibitor into Glioma Cells and Neurons †

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Abstract: Obesity and glioblastoma multiforme (GB) are two unmet medical needs where effective therapies are lacking. Carnitine palmitoyl transferase 1 (CPT1), an enzyme catalyzing the rate-limiting step in fatty acid oxidation (FAO), is a viable target for both diseases. C75, a fatty acid synthase (FAS) inhibitor, forms an adduct with coenzyme A (CoA) to form C75-CoA, which is a strong competitive inhibitor to CPT1 that is selective in its target. However, it is polar and charged, having low cell membrane permeability, and therefore needing a delivery system for intracellular transport. (±)-C75-CoA and its enantio-separated forms (+)- and (−)-C75-CoA were used to form poly-ion complex (PIC) micelles with the cationic block co-polymer PEG-PAsp(DET). The drug and polymer were mixed in a 1:1 anion/cation ratio to give 50–70 nm micelles with a unimodal size profile and narrow polydispersity. Size was maintained upon introduction of physiological saline. Micellar (±)-, (+)-, and (−)-C75-CoA were all significantly more cytotoxic compared to the respective free drugs in U87MG. We examined whether C75-CoA inhibits FAO by measuring ATP concentrations in U87MG and GT1-7. ATP generation was found to be hampered after adding C75-CoA in both cell types, with micelle-treated cells producing significantly lower ATP than those treated with free drug, suggesting that the effective intracellular delivery of C75-CoA leads to a more pronounced FAO inhibition. A fluorescent CoA derivative, Fluor-CoA, also yielded monodisperse micelles similar to C75-CoA. Micellar internalization was significantly greater than that of the free dye. Uptake of both increased with time, with this effect is more pronounced in U87MG than GT1-7. The %Fluor-CoA+ cells were also expressively higher for the micelle across cell lines. From this data, it can be convincingly concluded that neuronal and glioma cellular uptake of micelles is superior to that of the free dye, validating the need for cellular delivery systems for anionic, CoA-type molecules. The micellar form neutralized the negative charge of the cargo, promoting transport into the cell. These outcomes strongly support the effectiveness of using a PIC micelle-type system to deliver anionic small molecules into glioma cells and neurons meant to inhibit enzymes such as CPT1, for future applications in diseases like obesity and cancer.