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Development of selective cannabinoid nanoparticles to target the atheroma plaque

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1. Introduction

Atherosclerosis is the major cause of cardiovascular disease death in the developed world, for which there is no specific treatment [1]. Currently, the endothelial dysfunction and the inflammatory process in atherosclerosis are related with the actions of the endocannabinoid system. Cannabinoid receptor type 2 (CB2) is expressed in immune cells and is characterized for its anti-inflammatory properties, introducing CB2 agonists as a potential treatment [2, 3]. Given that these molecules have high lipophilicity and low availability, our research group has been exploring a platform of biodegradable, biocompatible and polymeric nanoparticles (NPs) as selective CB2 agonist delivery systems. For this purpose, we selected JWH-133, a synthetic, selective and potent CB2 agonist. Moreover, since cell adhesion molecule VCAM-1 was highly expressed in the vascular endothelium of the atheroma plaque [4], NPs were functionalized with a VCAM-1 binding peptide (VCAM-1 BP) to target nanosystems in the atherosclerotic region (Fig. 1).

2. Materials and methods

2.1 NPs production

Polymeric NPs were produced by nanoprecipitation method previously described(5) using a mixture of three types of poly(lactide-co-glycolic): (i) PLGA; (ii) poly(lactide-co-glycolide)-b-poly (ethylene glycol) (PLGA-PEG) and (iii) poly(lactide-co-glycolide)-b-poly (ethylene glycol)-maleimide (PLGA-PEG-Mal) polymers at different ratios.

2.2. Drug loading

The cannabinoid was loaded to the NPs with a drug loading (DL, %) of 15 % drug/polymer concentration (w/w). JWH-133 loading to the NPs was determined

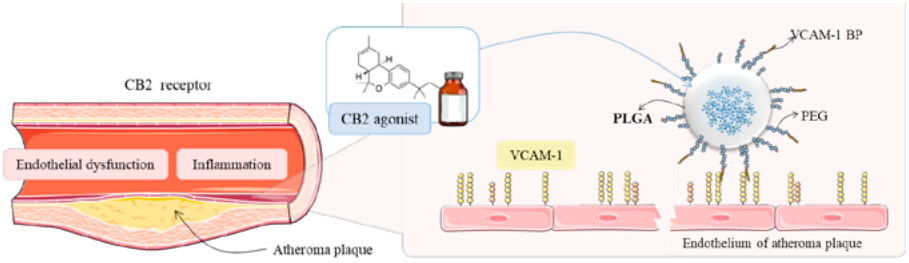

Fig. 1. Targeting of selective CB2 NPs to atherosclerotic regions through the interaction with the VCAM-1 adhesion molecules

by a reverse phase-high performance liquid chromatography (RP-HPLC) method. Drug incorporation to the NPs was indicated as entrapment efficiency (EE, %).

2.3. NPs functionalization

NPs prepared using 85:5:10 w/w ratio of PLGA:PLGA-PEG:PLGA-PEG-Mal, were functionalized with VCAM-1 BP. After 2h of NPs conjugation in HEPES 10mM/EDTA 0.4mM buffer, conjugation efficiency (CE%) was measured by microBCA assay.

2.4. In vitro cytotoxic activity

Cell viability after incubation of NPs during 24h was evaluated by MTT assays on human umbilical vein endothelial cells (HUVEC).

2.5. Cell uptake of functionalized NPs

In vitro cell uptake was studied using fluorescently labelled NPs (Nile Red-NPs) by confocal microscopy in tumor necrosis factor alpha (TNFα) stimulated cells.

3. Results and Discussion

The NPs were in 150-200 nm of diameter, showed spherical morphology, negative surface charge and, high encapsulation efficiency of JWH-133. After conjugation, functionalized NPs maintained their shape and size.

Cell viability assays on HUVEC indicated low or non-toxicity for both blank and loaded-JWH-133 NPs. In contrast, cell viability was compromised when free CB2 agonist was incubated at high concentrations, indicating the positive impact of drug nanoencapsulation.

For cell NP uptake, TNFα stimulation resulted in a pro-inflammatory profile that mimicked the pathogenic condition. In vitro stimulated HUVEC expressed high levels of VCAM-1, resulting in increased recruitment and cell uptake of functionalised NPs in comparison of non-stimulated cells.

4. Conclusions

These preliminary results highlight the potential of formulated PLGA-NPs as functionalized selective delivery system for the vehiclization of CB2 agonists to target atheroma regions.

Acknowledgments

The authors would like to thank Biology Service of CITIUS for the assistance and equipment. This work has been supported by the Programa Operativo FEDER 2014-2020, the Consejería de Economía y Conocimiento de la Junta de Andalucía (US-1263053), and the Plan Propio of the University of Seville (Acción I.5).

References

1. Bergheanu SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis: Current view and future perspective on lipoprotein modification treatment. Netherlands Hear J. 2017;25(4):231–42.
2. Hoyer FF, Steinmetz M, Zimmer S, Becker A, Lütjohann D, Buchalla R, et al. Atheroprotection via cannabinoid receptor-2 is mediated by circulating and vascular cells in vivo. J Mol Cell Cardiol [Internet]. 2011;51(6):1007–14. Available from: http://dx.doi.org/10.1016/j.yjmcc.2011.08.008
3. Steffens S, Veillard NR, Arnaud C, Pelli G, Burger F, Staub C, et al. Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. Nature. 2005;434(7034):782–6.
4. Yin M, Li C, jiang J, Le J, Luo B, Yang F, et al. Cell adhesion molecule-mediated therapeutic strategies in atherosclerosis: From a biological basis and molecular mechanism to drug delivery nanosystems. Biochem Pharmacol. 2021;186(February).
5. Durán-Lobato M, Martín-Banderas L, Gonçalves LMD, Fernández-Arévalo M, Almeida AJ. Comparative study of chitosan- and PEG-coated lipid and PLGA nanoparticles as oral delivery systems for cannabinoids. J Nanoparticle Res. 2015;17(2).

Este trabajo debe ser citado como:

Martín Navarro L, Clara Cala CM, Herrera González MD, Álvarez Fuentes J, Martín Banderas L. Development of selective cannabinoid nanoparticles to target the atheroma plaque. Rev Esp Cien Farm. 2021;2(2):79-80.