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# Lipid nanocapsules for the nose-to-brain delivery of the anti-inflammatory bioactive lipid $PGD_2$-G

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## Abstract

Here, prostaglandin $D_2$-glycerol ester ($PGD_2$-G) was selected to target neuroinflammation. As $PGD_2$-G is reported to have a short plasmatic half-life, we propose to use lipid nanocapsules (LNC) as vehicle to safely transport $PGD_2$-G to the central nervous system (CNS). $PGD_2$-G-loaded LNC ($PGD_2$-G-LNC) reduced pro-inflammatory cytokine expression in activated microglial cells, even so after crossing a primary olfactory cell monolayer. A single nasal administration of $PGD_2$-G-LNC in lipopolysaccharide (LPS)-treated mice reduced pro-inflammatory cytokine expression in the olfactory bulb. Coating LNC's surface with a cell-penetrating peptide, transactivator of transcription (TAT), increased its accumulation in the brain. Although TAT-coated $PGD_2$-G-LNC modestly exerted its anti-inflammatory effect in a mouse model of multiple sclerosis similar to free $PGD_2$-G after nasal administration, TAT-coated LNC surprisingly reduced the expression of pro-inflammatory chemokines in the CNS. These data propose LNC as an interesting drug delivery tool and TAT-coated $PGD_2$-G-LNC remains a good candidate, in need of further work.


*Keywords:* Multiple sclerosis; Nasal administration; Neuroinflammation; Lipid nanoparticles; Bioactive lipids

## Introduction

Neuroinflammation is a pathophysiological process associated with many diseases of the central nervous system (CNS), including multiple sclerosis (MS).[1] Though initially beneficial for the overall protection of the brain, chronic inflammation plays an important role in the onset and progression of MS[2–4] and is considered a main contributor to impaired remyelination.[5]

Several lipids are important regulators of immunity and inflammation including prostaglandin $D_2$-Glycerol ester ($PGD_2$-G). $PGD_2$-G is a bioactive lipid with strong anti-inflammatory properties demonstrated *in vitro*[6] and *in vivo*,[7,8] derived from the oxygenation of the endocannabinoid 2-arachidonoylglycerol

*Abbreviations:* 15d-$PGJ_2$-G, 15-Deoxy-delta12,14-Prostaglandin $J_2$-glycerol ester; **aCSF**, artificial cerebrospinal fluid; **BV2**, Murine microglial cell line; **DiD**, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindodicarbocyanine 4-chlorobenzenesulfonate; **DiR**, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide; **DP1**, D-type prostanoid receptor 1; **EAE**, Experimental autoimmune encephalomyelitis; **IVIS**, *In vivo* imaging system; **LNC**, Lipid nanocapsules; **LNC TAT**, TAT-coated LNC; **MS**, Multiple sclerosis; **MCP-1**, Monocyte chemoattractant protein-1; **MIP-1α**, Macrophage inflammatory protein-1 alpha; **MIP-1β**, Macrophage inflammatory protein-1 beta; **MOG**, Myelin-oligodendrocyte glycoprotein; **$PGD_2$-G**, Prostaglandin $D_2$-glycerol ester; **$PGD_2$-G-LNC**, $PGD_2$-G-loaded LNC; **$PGD_2$-G-LNC TAT**, TAT-coated $PGD_2$-G-LNC; **PTX**, Pertussis toxin; **TAT**, Transactivator of transcription; **UPLC/MS/MS**, Ultraperformance liquid chromatography-tandem mass spectrometry; **ZP**, Zeta-potential.

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