



Exendin-4 Anti-Inflammatory Pleiotropy: Decoding Molecular Signaling Pathways from Metabolic Control to Tissue Protection

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Abstract Background: Exendin-4 (Ex-4), a stable glucagon-like peptide-1 receptor (GLP-1R) agonist, has transcended its initial role as a glycemic regulator to become a potent mediator of cellular inflammation. This review synthesizes the molecular crosstalk between Ex-4 and tissue-specific inflammatory environments, emphasizing its therapeutic trajectory. **Summary:** At the cellular level, Ex-4 exerts anti-inflammatory effects primarily through the inhibition of the NF- κ B and NLRP3 inflammasome pathways and the activation of the SIRT1/AMPK axis. In the central nervous system, it facilitates a phenotypic shift from pro-inflammatory M1 to reparative M2 microglia. In peripheral tissues, it attenuates fibrosis via TGF- β /Smad suppression and restores airway homeostasis through the PKA-PPAR γ -FOXA2 pathway. While there were signaled challenges in motor-score endpoints for Parkinson's disease, the peptide shows robust efficacy in treating Idiopathic Intracranial Hypertension (IIH) and polycystic ovary syndrome (PCOS). **Conclusion:** Exendin-4 remains a cornerstone of metabolic-inflammatory research. Future therapeutic success likely hinges on the development of "smart" delivery systems-such as ligand-functionalized nanoparticles and sustained-release hydrogels-to optimize bioavailability and minimize systemic side effects (Figure 1).

Key Words Exendin-4, GLP-1 Receptor, Anti-inflammatory, Neuroprotection, SIRT1, NF- κ B

INTRODUCTION

Exendin-4 (Ex-4), clinically known in its synthetic form as exenatide, is a robust agonist of the glucagon-like peptide-1 receptor (GLP-1R) [1]. While it shares only 53% sequence homology with human GLP-1, its resistance to dipeptidyl peptidase-4 (DPP-4) degradation grants it a significantly longer half-life, making it a superior candidate for chronic therapeutic use [2]. Initially approved for the treatment of Type 2 Diabetes Mellitus (T2DM) due to its insulinotropic effects, recent evidence has shifted the focus toward its potent anti-inflammatory and cytoprotective capabilities [3, 4].

Inflammation is a common denominator in the progression of numerous chronic pathologies, from Alzheimer's disease to atherosclerosis [5, 6]. Exendin-4 has

been shown to traverse the blood-brain barrier (BBB) and exert direct effects on immune cells, including macrophages and microglia, thereby modulating the systemic and local inflammatory microenvironment [5, 7].

Molecular Mechanisms of Anti-inflammatory Action

The anti-inflammatory efficacy of Exendin-4 is rooted in its ability to regulate diverse intracellular signaling cascades.

Inhibition of the NF- κ B and NLRP3 Pathways

Activation of GLP-1R by Exendin-4 leads to a reduction in the phosphorylation of the p65 subunit of nuclear factor-kappa B (NF- κ B), a master regulator of pro-inflammatory gene expression [8]. Furthermore, Ex-4 has been shown to

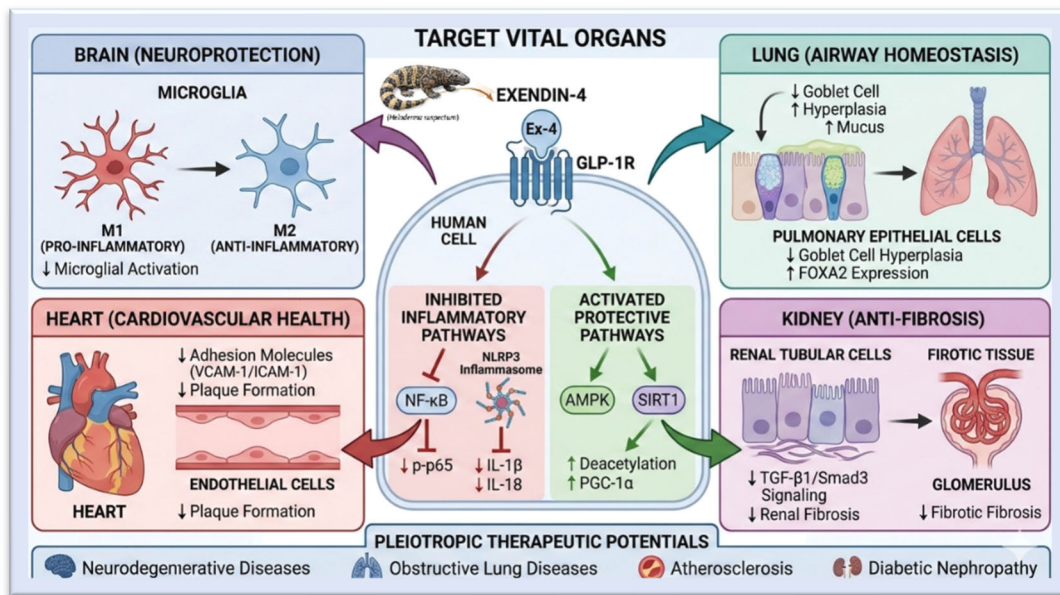


Figure 1: Graphical Abstract

inhibit the assembly of the NLRP3 inflammasome, subsequently reducing the maturation and release of pro-inflammatory cytokines such as IL-1 β and IL-18 [3].

Activation of SIRT1 and AMPK

Exendin-4 upregulates Silent Information Regulator 1 (SIRT1) and Adenosine Monophosphate-activated Protein Kinase (AMPK) signaling [9,10]. In hepatic and renal models, this axis is critical for reducing endoplasmic reticulum (ER) stress and lipotoxicity-induced inflammation [10,11]. SIRT1 activation also facilitates the deacetylation of NF- κ B, further suppressing the inflammatory response [9].

Modulation of MAPK and JNK

While Exendin-4 can transiently activate Mitogen-Activated Protein Kinases (MAPKs) to promote cell survival and differentiation [12], chronic administration in inflammatory contexts typically attenuates the phosphorylation of p38 MAPK and c-Jun N-terminal kinase (JNK) [6,13]. This suppression is vital in protecting pancreatic β -cells and neurons from cytokine-induced apoptosis [13,14].

Therapeutic Potential Based on Metabolic Control

Therapeutic Potential in Neurodegenerative Diseases:

Neuroinflammation is a hallmark of Parkinson's Disease (PD) and Alzheimer's Disease (AD). Exendin-4 has shown remarkable promise as a disease-modifying agent in these conditions:

- **Parkinson's Disease:** Some clinical trials have demonstrated that Exendin-4 can improve motor and cognitive functions in PD patients [8]. Mechanistically, it promotes microglial polarization from the pro-inflammatory M1 phenotype to the reparative M2 phenotype [7].

- **Alzheimer's Disease:** In AD models, Ex-4 reduces amyloid- β (A β) accumulation and suppresses microglial activation, thereby preserving synaptic integrity [8,15].
- **Ischemic Stroke:** Exendin-4 treatment after stroke has been shown to reduce brain water content and Evans blue extravasation by preserving BBB integrity via GLP-1R/AMPK-dependent inhibition of MMP-9 [7,8].

Pulmonary and Respiratory Health

Recent studies have identified GLP-1R expression in the lungs, positioning Exendin-4 as a potential treatment for obstructive airway diseases [4,15]:

- **Asthma and COPD:** Exendin-4 restores airway mucus homeostasis through the PKA-PPAR γ -FOXA2 signaling pathway, reducing the excessive mucus production characteristic of chronic obstructive pulmonary disease (COPD) [15].
- **Pneumonia:** In diabetic models of pneumonia, Exendin-4 improves outcomes by blocking T1R2/T1R3-mediated inflammatory responses and reducing pathogen accumulation [1].

Cardiovascular and Renal Protection

Exendin-4 exerts protective effects on the vasculature and kidneys by mitigating oxidative stress and inflammatory cell infiltration:

- **Atherosclerosis:** It reduces macrophage adhesion to the endothelium, an early step in plaque formation, by downregulating adhesion molecules [6].
- **Diabetic Nephropathy:** In the kidney, Ex-4 attenuates lipid accumulation and fibrosis by activating the SIRT1/AMPK pathway and reducing pro-inflammatory cytokine levels in the renal cortex [10].

Systemic Inflammation and Sepsis

In models of acute systemic inflammation induced by lipopolysaccharide (LPS), Exendin-4 administration significantly decreases circulating concentrations of TNF- α , IL-6 and IFN γ . Interestingly, it also modulates neutropenia and prevents the hypoglycemia often associated with early sepsis, suggesting a role in stabilizing the host response during critical illness [16].

Conceivable Tissue Protection

Neuroprotection: The Microglial Switch: In the Central Nervous System (CNS), Ex-4 operates primarily by shifting the polarization of microglia-the brain's resident immune cells:

- **Pathway:** Upon crossing the blood-brain barrier, Ex-4 binds to GLP-1R on microglia, triggering the cAMP/PKA (protein kinase A) pathway [3,7]
- **Mechanism:** This activation inhibits the translocation of the NF- κ B p65 subunit into the nucleus. Consequently, the production of pro-inflammatory mediators like TNF- α and NO (nitric oxide) is slashed [8]
- **The M1/M2 Shift:** Ex-4 promotes the M2 phenotype (anti-inflammatory/reparative) over the M1 phenotype (pro-inflammatory). This is mediated via the PI3K/Akt signaling axis, which enhances the expression of neurotrophic factors like BDNF [3,5]

Cardiovascular System: Vascular Integrity

Ex-4 mitigates atherosclerosis and myocardial injury by targeting the endothelium and cardiac macrophages:

- **AMPK/SIRT1 Axis:** Ex-4 activates AMPK (AMP-activated protein kinase), which in turn upregulates SIRT1. This duo is critical for inhibiting the NLRP3 inflammasome [10]
- **Adhesion Molecule Suppression:** By inhibiting the NF- κ B pathway in endothelial cells, Ex-4 reduces the expression of VCAM-1 and ICAM-1. This prevents the "velcro effect" where monocytes stick to vessel walls, effectively slowing plaque formation [6]
- **Oxidative Stress:** Ex-4 enhances the activity of antioxidant enzymes like Superoxide Dismutase (SOD) via the Epac/Rap1 pathway, protecting cardiomyocytes from oxidative bursts during ischemia-reperfusion [2]

Renal Protection: Defeating Fibrosis

In the kidneys, inflammation often leads to irreversible fibrosis. Ex-4 steps in as a "fibro-suppressant":

- **TGF- β /Smad Signaling:** One of the most vital pathways Ex-4 modulates is the inhibition of TGF- β 1 (transforming growth factor-beta 1). By suppressing Smad3 phosphorylation, Ex-4 prevents the transition of healthy renal cells into myofibroblasts [10,17]

- **MCP-1 Inhibition:** Ex-4 reduces the levels of Monocyte Chemoattractant Protein-1 (MCP-1) in the renal cortex. This prevents the mass migration of macrophages into the kidneys, which is a primary driver of diabetic nephropathy [10]
- **Lipid Homeostasis:** Through the SIRT1/PGC-1 α axis, Ex-4 improves mitochondrial biogenesis in tubular cells, reducing the "lipotoxicity" that triggers local inflammatory responses [9,10]

Pulmonary System: Mucus and Airway Tone

The lungs possess a high density of GLP-1Rs, particularly in the airway smooth muscle and epithelial cells:

- **The PKA-PPAR γ -FOXA2 Axis:** This is perhaps the most unique pathway for Ex-4. In chronic obstructive pulmonary disease (COPD) or asthma, the transcription factor FOXA2 is often suppressed, leading to mucus overproduction (goblet cell hyperplasia). Ex-4 activates PKA, which stabilizes PPAR γ , ultimately restoring FOXA2 expression and shutting down the MUC5AC gene (the primary mucus gene) [4]
- **T1R2/T1R3 Modulation:** In cases of bacterial pneumonia, Ex-4 has been shown to block the T1R2/T1R3 "sweet taste" receptors on the airway surface, which bacteria often hijack to suppress host immune defense [1]

Summary of molecular targets is shown in Table 1.

Future Perspectives: Engineering the Next Generation of Exendin-4 Therapies

While the molecular efficacy of Exendin-4 (Ex-4) across vital organs is well-documented, its clinical translation faces hurdles: a relatively short half-life compared to weekly GLP-1R agonists, gastrointestinal side effects and the challenge of achieving high therapeutic concentrations in the central nervous system (CNS) [2,3]. The future of Ex-4 therapy lies in the intersection of molecular biology and advanced bioengineering.

Nanotechnology and Enhanced CNS Delivery

To fully harness the neuroprotective potential of Ex-4 in diseases like Alzheimer's and Parkinson's, crossing the blood-brain barrier (BBB) more efficiently is paramount:

- **Targeted Nanocarriers:** Current research is pivoting toward ligand-functionalized nanoparticles (e.g., gold, PLGA or liposomes) that can be "tagged" to recognize specific receptors on the BBB [18]. These carriers protect the peptide from peripheral degradation and ensure a concentrated release directly into the brain parenchyma
- **Intranasal Delivery:** Future clinical models are exploring the nose-to-brain pathway, utilizing

Table 1: Summary of Molecular Targets by Organ

Organ	Primary Signaling Axis	Key Inflammatory Target	Therapeutic Outcome
Brain	cAMP/PKA/PI3K-Akt	NF- κ B/M1 Microglia	Neuroprotection (AD/PD)
Heart	AMPK/SIRT1/Epac	NLRP3/VCAM-1	Atherosclerosis reduction
Kidney	SIRT1/PGC-1 α	TGF- β 1/MCP-1	Anti-fibrotic/Nephroprotection
Lungs	PKA/PPAR γ /FOXA2	MUC5AC/IL-8	Airway homeostasis (COPD)

mucoadhesive nanogels to bypass the systemic circulation entirely, thereby reducing the nausea and vomiting often associated with GLP-1R activation [5,7]

Sustained-Release Systems and Localized Therapy

Chronic inflammatory conditions like diabetic nephropathy or COPD require long-term, stable drug levels:

- **Injectable Hydrogels:** Researchers are developing thermosensitive hydrogels that can be injected subcutaneously or even locally (near a damaged organ). These gels act as a reservoir, releasing Ex-4 over weeks or months, maintaining the activation of the AMPK/SIRT1 axis without the "peaks and valleys" of daily injections [10,19]
- **Oral Delivery Breakthroughs:** Engineering pH-sensitive nanocapsules or using "microneedle" capsules could revolutionize Ex-4 therapy, shifting it from an injectable to an oral daily pill, which would significantly increase patient compliance in early-stage inflammatory diseases [20]

Synergistic Combination Therapies

The next frontier involves "molecular cocktails" where Ex-4 is paired with other small molecules to create a synergistic anti-inflammatory effect:

- **Ex-4+SGLT2 Inhibitors:** Preliminary data suggest that combining Ex-4 with SGLT2 inhibitors may provide superior renal protection by simultaneously targeting hemodynamic stress and the TGF- β /Smad inflammatory pathway [10]
- **Ex-4+Curcumin/Resveratrol:** Co-delivery with natural SIRT1 activators could amplify the deacetylation of NF- κ B, leading to a more profound suppression of the "cytokine storm" in systemic conditions like sepsis [9,16]

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