What effect does GLP1-RA's have on the mTOR system, use only reputable journals as a source, no clinics, influencers, blogs or youtube video

GLP-1 receptor agonists (GLP-1 RAs) can both activate and inhibit components of the mTOR pathway depending on tissue, context, and dose, largely through cAMP/PKA, Akt, and AMPK signaling. These context-specific effects translate into changes in autophagy, cell growth, mitochondrial function, and inflammation rather than a simple “mTOR on” or “mTOR off” effect.[1] [2] [3] [4] [5] [6] [7]

Direct effects on mTOR complexes

- In β-cell and neuronal models, GLP-1R activation (e.g., with liraglutide) stimulates mTORC1 signaling via PKA-dependent phosphorylation of Raptor, and also via cAMP-Akt activation, defining a GLP-1R–PKA–mTORC1 axis that contributes to weight loss and metabolic actions.[8] [1]
- Experimental work in cardiomyocytes and vascular cells indicates GLP-1R agonists (e.g., exendin-4, liraglutide) engage mTOR signaling as part of their protective response to hyperglycemia or ischemic stress, although the net effect (stimulation vs modulation) depends on the injury model.[6] [7]

AMPK–mTOR–autophagy axis

- In a remnant-kidney rat model, liraglutide promoted autophagy and renoprotection through modulation of the AMPK/mTOR pathway, consistent with a shift toward AMPK activation and relative mTOR suppression in that context.[2]
- In type 2 diabetes–related cognitive impairment, liraglutide reduced elevated hippocampal phospho-mTOR and restored AMPK and PI3K/Akt signaling, improving autophagic flux and cognition, suggesting mTOR down-regulation in injured brain tissue.[4]

PI3K/Akt/mTOR and tissue-specific autophagy

- In a PCOS mouse model, semaglutide improved ovarian function and oxidative stress while altering PI3K/Akt/mTOR signaling, with data consistent with mitigation of excessive autophagy and normalization of mTOR pathway activity.[3]
- In hypoxia/reoxygenation-injured cardiomyocytes, semaglutide enhanced PINK1/Parkin-dependent mitophagy and overall autophagy, with the authors proposing regulation of key autophagy controllers including mTOR and AMPK as a likely mechanism.[5]

Inflammation, vascular effects, and mTOR

- In vascular endothelial models of Kawasaki disease, liraglutide protected cells via an AMPK/mTOR/NF-κB pathway, in which AMPK activation and downstream mTOR signaling collectively reduced inflammatory responses.[7]
- In cardiac models of high-glucose injury, exendin-4's cardioprotective actions involve GLP-1R–mTOR signaling, tying mTOR modulation to preservation of mitochondrial structure and function under metabolic stress.[6]

Overall mechanistic picture

- GLP-1 RAs do not exert a uniform anabolic "mTOR upregulation"; instead, they fine-tune mTOR activity via PKA, Akt, and AMPK, often activating mTORC1 in metabolically active cells while dampening pathological overactivation in injured tissues to restore autophagy and cellular homeostasis.[1] [2] [3] [4] [5] [7] [6]
- These bidirectional effects on the **mTOR** system likely underlie part of the observed benefits of GLP-1 RAs on weight, mitochondrial health, organ protection, and inflammation, but the net effect is highly tissue- and disease-specific and remains an active area of research.[9] [10] [11]

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How does GLP1RA signaling engage PKA AMPK and mTOR pathways

GLP-1 receptor agonists (GLP-1RAs) signal through a G_s–cAMP hub that activates PKA, which can then modulate AMPK and mTOR (especially mTORC1) in a context-dependent manner. The net effect is a **PKA**-driven mTORC1 activation axis in some cells, with parallel AMPK–mTOR crosstalk that can either restrain or be restrained by mTORC1 depending on metabolic state.[16] [17] [18] [19] [20] [21] [22]

Step 1: GLP-1R → cAMP → PKA

- GLP-1R is a class B G-protein-coupled receptor mainly coupled to G_s; agonist binding promotes $G_s\alpha$ activation, adenylyl cyclase stimulation, and increased intracellular cAMP.[23] [16]
- cAMP then activates PKA (and Epac) in spatially restricted microdomains, so GLP-1R signaling produces compartmentalized PKA activity that differs from classical β-adrenergic cAMP/PKA signaling.[24] [25] [16] [23]

Step 2: PKA → mTORC1 (via Raptor)

- In cell and mouse models, liraglutide-induced GLP-1R activation increases mTORC1 signaling (e.g., S6 phosphorylation), and this requires PKA activity.[18] [19]
- Mechanistically, PKA directly phosphorylates the mTORC1 scaffold protein Raptor at Ser791 after GLP-1R stimulation, forming a GLP-1R–PKA–Raptor–mTORC1 axis that contributes to

liraglutide-induced weight loss in vivo; mice with a Ser791Ala (PKA-resistant) Raptor have a blunted weight-loss response to liraglutide.[26] [19] [18]

Step 3: AMPK–mTOR bidirectional crosstalk

- Canonically, AMPK inhibits mTORC1 by phosphorylating TSC2 and Raptor, thereby suppressing protein synthesis and stimulating autophagy.[20] [21]
- GLP-1R–PKA–mTORC1 activation can, in principle, reduce AMPK activity (since mTORC1 can inhibit AMPK), while AMPK activation would antagonize mTORC1; Le et al. explicitly note that GLP-1R-mediated mTORC1 activation could occur by reducing AMPK activity and that mTORC1 can feed back to inhibit AMPK.[27] [18]

Tissue examples of AMPK/mTOR involvement

- In obese mouse liver, semaglutide's beneficial effects involve modulation of the mTORC1/AMPK pathway, consistent with coordinated changes in nutrient-sensing and autophagy signaling downstream of GLP-1R.[22]
- Reviews of AMPK/mTOR biology emphasize that any GLP-1RA-driven changes in cellular energy state (e.g., improved insulin sensitivity or altered nutrient flux) will secondarily tune AMPK, which then feeds into mTORC1 control, adding a metabolic layer on top of the direct PKA–Raptor mechanism.[21] [20] [22]

Integrated signaling model

- At the receptor level, GLP-1RAs:
  1. activate G_s → cAMP → PKA;
  2. PKA directly phosphorylates Raptor to stimulate mTORC1;
  3. mTORC1 and AMPK interact in a feedback loop, so GLP-1R signaling can either suppress or be constrained by AMPK depending on cellular energy and stress.[19] [16] [18] [20] [21] [22]
- This integrated network explains how GLP-1RAs can simultaneously promote mTORC1-linked anabolic/weight-loss programs in some tissues while engaging AMPK-mTOR circuitry involved in autophagy and stress resistance in others.[18] [20] [21] [22]

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