Mitochondrial GPCRs and the Negotiation of Adaptation

A systems-biology hypothesis linking host signaling, state-dependent mitochondrial regulation, and metabolic receptivity

A hypothesis paper with an illustrative self-tracked exercise observation

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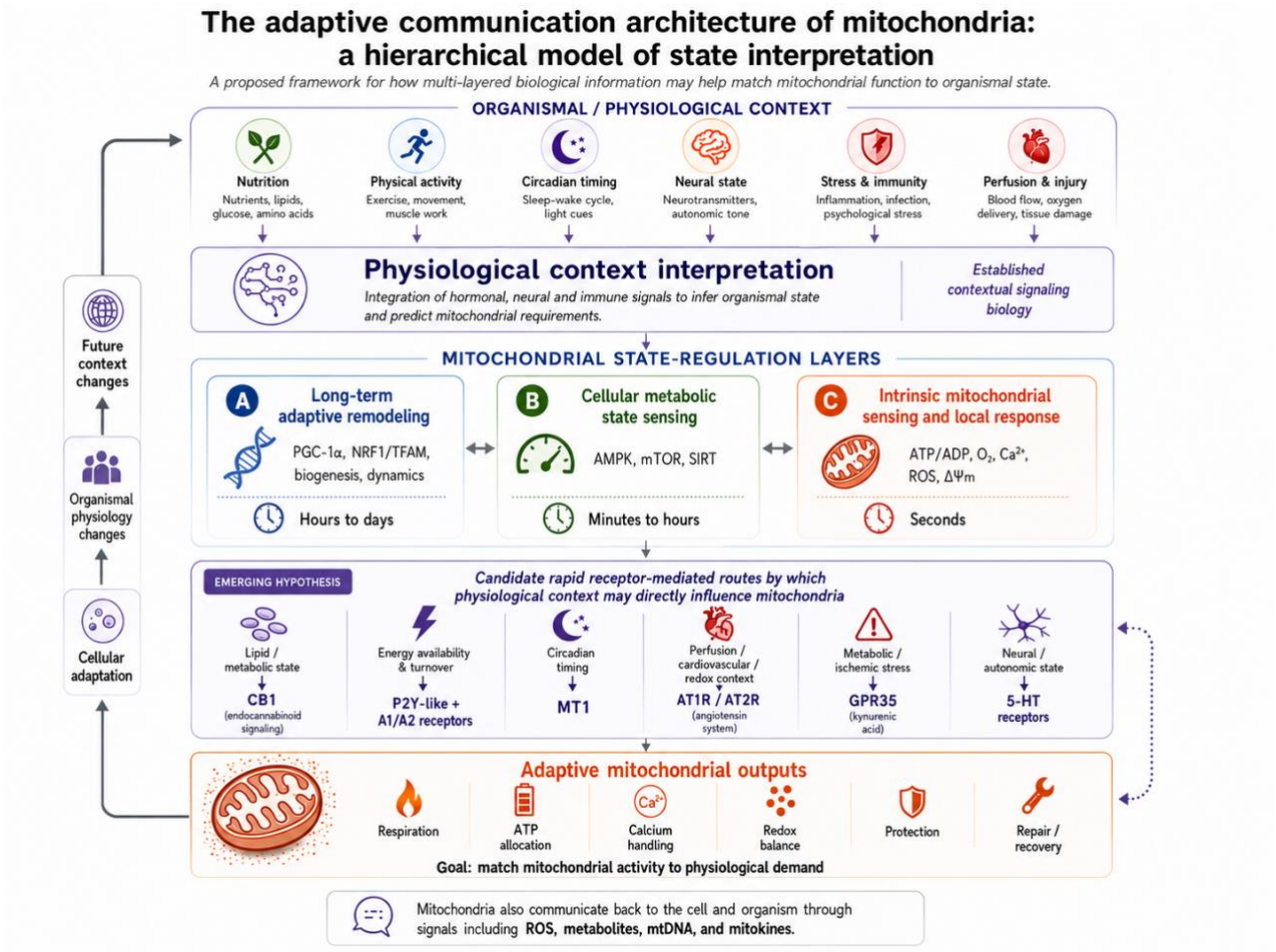
Abstract

Mitochondria can sense their immediate chemical environment: ATP and ADP, oxygen, calcium, redox state, substrate availability, and membrane potential. Yet those signals do not by themselves explain why energetic demand has changed, whether the cell is in a nutrient-rich, ischemic, inflammatory, circadian, neural, or stress-related state, or whether the appropriate response is acceleration, restraint, protection, or repair. This paper advances the hypothesis that mitochondrial G protein-coupled receptors (mGPCRs) provide part of that missing contextual layer. By locating host-cell signaling machinery at mitochondrial membranes, mGPCRs may allow biological state to modify mitochondrial respiration, calcium handling, redox signaling, ATP conservation, and cell-survival decisions.

At least thirteen full-length GPCRs have been reported in association with mitochondrial membranes, with highly variable levels of localization and functional evidence: CB1, MT1, AT1R, AT2R, P2Y1, P2Y2, P2Y12, A1, A2A, A2B, GPR35, 5-HT4, and 5-HT7. They arise from distinct ligand systems but converge on a limited set of mitochondrial control nodes. The central claim is not that every reported receptor is definitively mitochondrial in every tissue, nor that receptor activation is intrinsically beneficial or harmful. It is that the emerging repertoire is coherent enough to justify a testable systems-level model: host signaling may help mitochondria interpret physiological state and adjust their operating range accordingly.

The paper also presents an exploratory n=1 observation: after a substantial reduction in sustained THC exposure, low-volume, low-heart-rate running coincided with a marked rise in wearable-estimated VO_2max and a laboratory peak VO_2 near 63 $mL \cdot kg^{-1} \cdot min^{-1}$. This observation is non-causal and cannot establish CB1 or mitochondrial mechanism. It is included because it illustrates the proposed phenotype—different adaptive responses to a similar energetic challenge when the wider regulatory state may have changed. The intended contribution is a disciplined, category-defining framework for research, not a clinical claim or a substitute for individualized medical care.



Scope and evidence standard

This is a hypothesis-driven white paper, not a systematic review or a clinical guideline. “Mitochondrial” is used conservatively to mean a published report of receptor association with mitochondrial membranes, purified mitochondrial fractions, imaging, or mitochondrial-autonomous function. Evidence varies markedly across the list. Fractionation alone can be confounded by endoplasmic-reticulum, endosomal, or plasma-membrane contamination; claims become more persuasive when they are supported by orthogonal localization, organelle-selective pharmacology, genetic perturbation, and functional work in isolated mitochondria. The table is therefore an evidence map, not a declaration of equal certainty.

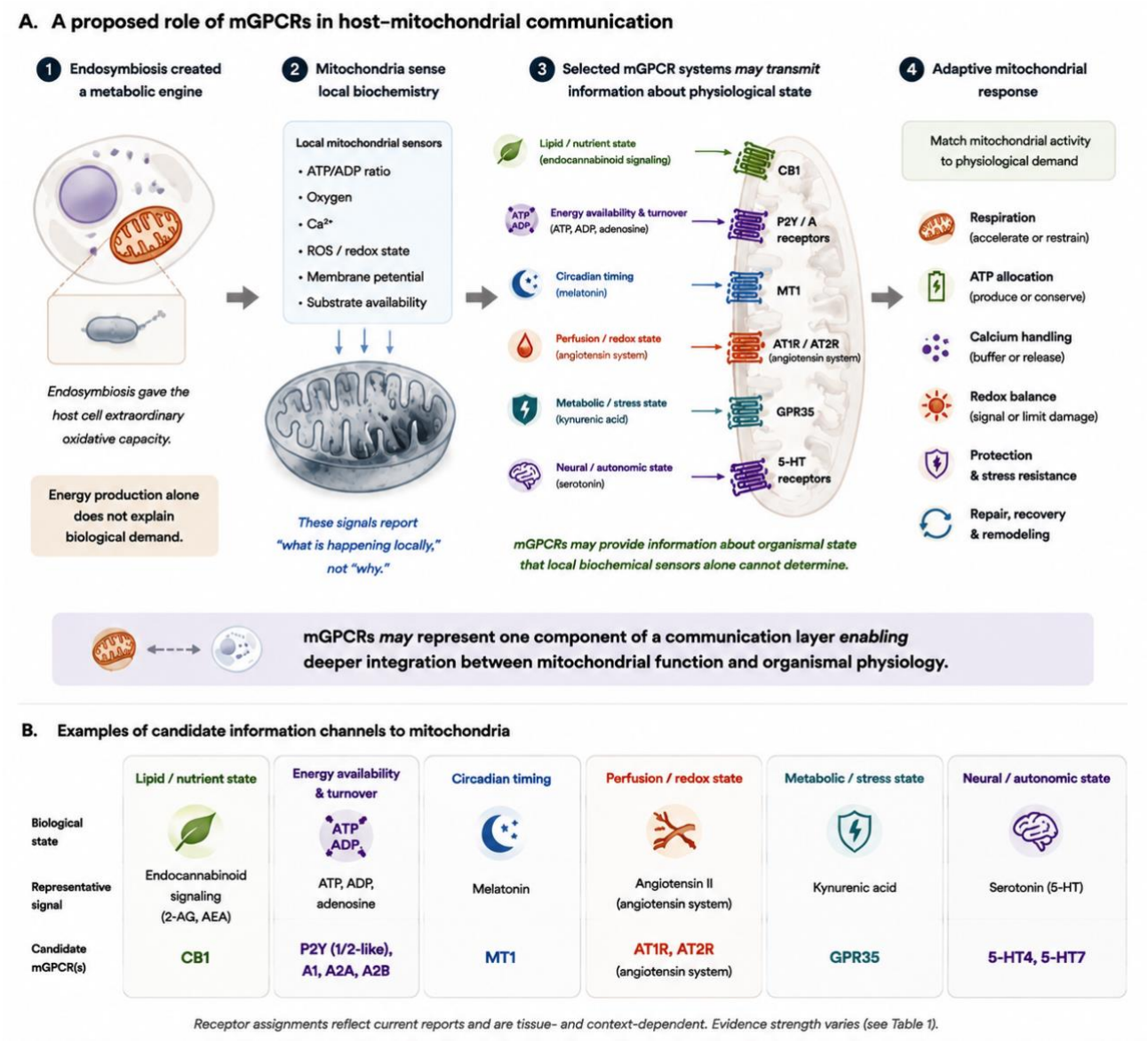


Figure 1. Conceptual model of mGPCR-mediated host–mitochondrial communication. mGPCRs may provide mitochondria with contextual information that complements local biochemical sensing, allowing mitochondrial activity to be adjusted according to physiological state rather than energetic demand alone. Candidate information channels include lipid/nutrient state, energy turnover, circadian timing, perfusion/redox status, metabolic stress, and neural/autonomic signaling. Receptor assignments reflect current evidence and remain tissue- and context-dependent.

1. The control problem created by endosymbiosis

The mitochondrial ancestor brought extraordinary oxidative capacity into the emerging eukaryotic cell. But energy production is only useful when it is coordinated with the needs of the host. Modern mitochondria must respond not simply to local fuel and oxygen, but to feeding, exercise, neural activity, perfusion, inflammation, circadian phase, and danger. Nuclear control of mitochondrial protein content solves part of this problem over hours to days. Dynamic signaling is needed for the seconds-to-minutes decisions that determine how existing mitochondrial machinery behaves now.

The proposed model is therefore straightforward: mitochondria already know what is happening chemically; mGPCRs may help tell them what the organism is asking them to do with it. GPCRs are well suited to this role because they provide ligand recognition, amplification, reversibility, desensitization, trafficking, and compartment-specific signaling. Their possible mitochondrial role is not to replace intrinsic bioenergetic sensing, but to contextualize it.

2. From biochemical state to physiological meaning

A fall in ATP can mean muscle contraction, sustained neural activity, immune activation, insufficient oxygen, or failure of supply. A rise in reactive oxygen species can be a training signal or an injury signal. These states require different mitochondrial responses. mGPCR ligands provide candidate context channels: nucleotides and adenosine relate to energetic turnover; angiotensin to perfusion and redox context; melatonin to time and survival context; serotonin to neural and autonomic state; kynurenic acid to metabolic, immune, and ischemic stress; and endocannabinoids to lipid, nutrient, neural, and stress-related state.

The biological objective is therefore not maximum respiration. It is sufficient energetic output at the lowest appropriate biological cost. Depending on the situation, restraint of respiratory flux can lower redox pressure, prevent calcium overload, conserve ATP, or preserve the conditions needed for recovery. A controller needs the capacity to move in both directions. The reported reciprocal effects of P2Y1/P2Y2 on mitochondrial calcium uptake and AT1R/AT2R on mitochondrial redox-respiratory pathways are notable in this regard (Belous et al., 2004; Abadir et al., 2011).

3. The reported mGPCR repertoire

The following table is the centerpiece of the hypothesis. It summarizes not only reported mitochondrial associations, but also the potential regulatory information each receptor system could provide if mitochondrial localization represents a functional signaling mechanism. “Proposed adaptive capability” is an interpretive column: it states the proposed systems-level function, not a proven evolutionary purpose.

Table 1. Reported full-length mitochondrial GPCRs: inputs, control nodes, and proposed added capability

Evidence status is intentionally qualitative. “Reported” means published localization/function data exist, not that the receptor has been validated in every tissue or model.

Receptor	Physiological information represented	Evidence tier	Reported mitochondrial association and context	Mitochondrial effector/control node	Reported mitochondrial consequence	Proposed adaptive capability
CB1	Endocannabinoid tone; lipid availability; nutrient state; neural activity; stress-related signaling	**Tier 1: Strong mechanistic evidence**	Mitochondrial CB1 populations have been reported in neuronal mitochondria and striated muscle. Functional studies demonstrate mitochondrial CB1 signaling rather than localization alone (Bénard et al., 2012; Mendizabal-Zubiaga et al., 2016).	Gi/o signaling; soluble adenylyl cyclase; cAMP/PKA signaling; respiratory complex I	Activation reduces complex-I-dependent respiration and alters ATP production in neuronal and muscle systems (Bénard et al., 2012; Hebert-Chatelain et al., 2016; Mendizabal-Zubiaga et al., 2016).	Provides a mechanism through which lipid-derived and metabolic context can adjust mitochondrial respiratory gain rather than simply respond to fuel availability.
MT1	Circadian timing; melatonin availability; cellular stress and survival state	**Tier 1: Strong mechanistic evidence**	MT1 has been reported on the outer mitochondrial membrane, with evidence for mitochondrial melatonin production and receptor-dependent mitochondrial signaling (Suofu et al., 2017).	GPCR signaling pathways; mitochondrial permeability transition; cytochrome-c release pathways	Reduces stress-induced cytochrome-c release and protects mitochondrial integrity under stress conditions (Suofu et al., 2017).	Provides temporal and stress-related context that may influence mitochondrial decisions between adaptation, protection, and apoptosis.
GPR35	Kynurenic acid signaling; metabolic stress; immune state; ischemic stress	**Tier 1: Strong mechanistic evidence**	GPR35 provides one of the strongest examples of state-dependent mitochondrial recruitment. Agonist activation promotes trafficking to the outer mitochondrial membrane during ischemic challenge (Wyant et al., 2022).	ATPIF1; ATP synthase organization and dimerization	Promotes ATP preservation during ischemic stress by regulating ATP synthase function (Wyant et al., 2022).	Enables conditional recruitment of mitochondrial protection when energetic integrity is threatened.
AT2R	Angiotensin signaling; perfusion state; cardiovascular stress; redox balance	**Tier 2A: Strong association with context-dependent function**	Mitochondrial AT2R localization has been reported, including inner mitochondrial membrane association. Functional mitochondrial angiotensin signaling has been demonstrated (Abadir et al., 2011; Valenzuela et al., 2016).	Mitochondrial nitric oxide signaling; respiratory complex I regulation	AT2R-associated nitric oxide signaling can reduce oxygen consumption and modulate respiratory activity (Abadir et al., 2011).	Provides a counter-regulatory mechanism through which cardiovascular and redox context may influence mitochondrial restraint and protection.

AT1R	Angiotensin signaling; vascular state; perfusion; oxidative stress	**Tier 2A: Strong association with context-dependent function**	Mitochondrial AT1R has been reported alongside AT2R within mitochondrial angiotensin systems. Functional consequences appear highly dependent on tissue and physiological context (Abadir et al., 2011; Valenzuela et al., 2016).	NOX4-associated signaling; mitochondrial ROS pathways	Associated with altered mitochondrial oxidative signaling and respiratory regulation (Abadir et al., 2011; Valenzuela et al., 2016).	May connect systemic cardiovascular information with mitochondrial redox state, but its adaptive versus pathological effects require careful contextual interpretation.
5-HT4	Serotonergic signaling; neural/autonomic state; cardiac stress response	**Tier 2A: Strong association with context-dependent function**	Mitochondrial 5-HT4 localization and functional regulation have been reported in cardiac models (Ma et al., 2016).	cAMP signaling; mitochondrial calcium handling; permeability transition pathways	Influences mitochondrial calcium dynamics, respiration, and stress tolerance (Ma et al., 2016).	Provides a potential route through which serotonergic and autonomic state influence mitochondrial energetic and survival decisions.
P2Y1-like / P2Y2-like receptors	ATP/ADP balance; nucleotide turnover; energetic demand	**Tier 2B: Emerging functional evidence**	Mitochondrial P2Y-like receptor activity has been reported in hepatocyte models. The original studies describe P2Y-like activity rather than definitive modern receptor assignment (Belous et al., 2004).	Mitochondrial calcium uptake pathways; MCU-related regulation	P2Y1-like and P2Y2-like signaling produced opposing effects on mitochondrial calcium uptake (Belous et al., 2004).	Provides a possible mechanism linking energetic demand and nucleotide state to calcium-dependent mitochondrial recruitment.
A1 adenosine receptor	ATP turnover; adenosine accumulation; hypoxia; metabolic stress	**Tier 2B: Emerging functional evidence**	Recent studies have reported mitochondrial localization and functional effects for adenosine receptors, including A1, in experimental systems (Sánchez-Melgar A et al., 2025).	Gi-linked cAMP pathways; respiratory regulation	Alters mitochondrial energetic output and respiratory responses (Sánchez-Melgar A et al., 2025).	Allows mitochondria to interpret ATP consumption and metabolic stress through the extracellular signal of adenosine.
A2A adenosine receptor	Adenosine abundance; inflammatory state; hypoxia; energetic workload	**Tier 2B: Emerging functional evidence**	Mitochondrial localization and functional effects have been reported (Sánchez-Melgar A et al., 2025).	Gs/cAMP signaling; mitochondrial coupling regulation	Influences respiratory efficiency and coupling behavior (Sánchez-Melgar A et al., 2025).	May allow adjustment between energetic efficiency and protective dissipation during metabolic stress.
A2B adenosine receptor	High adenosine states; ischemia; inflammatory stress	**Tier 2B: Emerging functional evidence**	Stress-associated mitochondrial localization/function has been reported (Sánchez-Melgar A et al., 2025).	cAMP/OXPHOS-related pathways	Alters mitochondrial energetic responses during stress conditions.	May function as a higher-threshold metabolic stress sensor linking severe energetic disturbance to mitochondrial adaptation.

P2Y12	ADP signaling; platelet, immune, and metabolic state	**Tier 3: Preliminary association**	Mitochondrial association has been suggested, but receptor-specific mitochondrial mechanisms remain insufficiently characterized.	Unresolved	Unresolved	Represents a possible additional nucleotide-sensitive mitochondrial signaling pathway requiring validation.
5-HT7	Serotonergic/neural signaling	**Tier 3: Preliminary association**	5-HT7 has been detected in mitochondrial membrane preparations, with preliminary functional effects reported on respiratory complex IV activity (Mitochondrial Membranes of Human SH-SY5Y Neuroblastoma Cells Express Serotonin 5-HT7 Receptor, 2021).	Complex IV/cytochrome-c oxidase	Reported modulation of complex IV activity, but physiological relevance remains unclear.	Represents a possible serotonergic input pathway to mitochondrial electron transport requiring independent validation.

The evidence hierarchy is important because mitochondrial GPCR biology remains an emerging field. Some receptors, including CB1, MT1, AT2R, and GPR35, are supported by convergent localization and functional evidence. Others represent promising candidates where mitochondrial association or function has been reported but requires further replication and mechanistic resolution. The purpose of this framework is therefore not to define a completed mitochondrial GPCR repertoire, but to identify a biologically coherent hypothesis: that selected host signaling systems may provide mitochondria with contextual information that influences how they respond to changing physiological demands. Importantly, the strongest version of this hypothesis does not require every reported mitochondrial GPCR to represent a validated organelle signaling pathway. It predicts that a subset of receptors will prove to form a distributed network through which physiological context is translated into mitochondrial adaptation.

4. What the repertoire suggests

Importantly, the proposed adaptive capabilities represent a systems-level interpretation of known receptor biology rather than demonstrated evolutionary functions. The table asks a forward-looking question: if mitochondrial receptors are retained because they provide contextual information, what biological variables do they allow mitochondria to interpret?

The list is heterogeneous, and it would be premature to treat it as a finished organelle proteome. Even so, the outputs are strikingly concentrated: complex I and IV activity, ATP synthase, calcium handling, cAMP/PKA, nitric oxide and reactive oxygen species, coupling, permeability transition, and cytochrome-c release. These are high-leverage variables that determine whether a mitochondrion accelerates, restrains, preserves ATP, tolerates a transient stressor, or enters a damage-related transition.

The inputs are similarly non-random-looking. Purines report energy availability and turnover. Angiotensin offers hemodynamic and redox context. Melatonin provides temporal and survival context. Serotonin conveys neural/autonomic context. Kynurenic acid links metabolic and ischemic stress to a direct mitochondrial protective response. Endocannabinoids add a lipid-derived context channel. This convergence is descriptive, not a formal statistical enrichment result; discovery bias and broad functional categories are real limitations. Still, it provides a clear prediction: a rigorous, blinded enrichment analysis should find that validated mGPCRs disproportionately represent state variables relevant to mitochondrial adaptation.

5. CB1 as a negotiator of adaptation

mtCB1 is one of the best-developed cases because its link to a defined respiratory mechanism is relatively direct. In neuronal mitochondria, CB1 activation reduces soluble-adenylyl-cyclase/cAMP/PKA signaling and decreases complex-I-dependent respiration (Bénard et al., 2012). A mitochondrial CB1 pool has also been described in striated muscle, where it regulates oxidative activity (Mendizabal-Zubiaga et al., 2016). This does not justify the simple conclusion that CB1 is “bad for mitochondria.” Respiratory restraint can be appropriate under some states and costly under others.

The more useful question is what endocannabinoid signaling contributes to mitochondrial interpretation of demand. Endocannabinoids carry information about membrane lipid state, nutrient availability, neural activity, stress, reward, and feeding-related physiology. On this view, CB1 is a negotiator of adaptation: it can help set how aggressively energetic resources are mobilized, how much respiratory intensity is appropriate, and when it is wiser to preserve flexibility for recovery. mtCB1 may function as a contextual gain control—not a universal brake, but one pathway through which mitochondria are prevented from treating every energetic demand as a command for maximal oxidative throughput. The pathology of prolonged tonic signaling may therefore be loss of dynamic range rather than a single-direction effect. A pathway that is chronically occupied, desensitized, or redistributed becomes less able to encode that something has changed.

This distinction matters for translation. Acute THC, chronic sustained exposure, endogenous phasic ligand signaling, and non-intoxicating cannabinoid interventions are not interchangeable. Neither the mGPCR

thesis nor the case observation below supports a generalized recommendation to start, stop, or change cannabis therapy. The hypothesis instead identifies a tractable research question: does sustained CB1-state perturbation modify the conversion of a standardized energetic challenge into subsequent adaptation?

6. Adjacent architecture: GOST proteins and organelle-centered state regulation

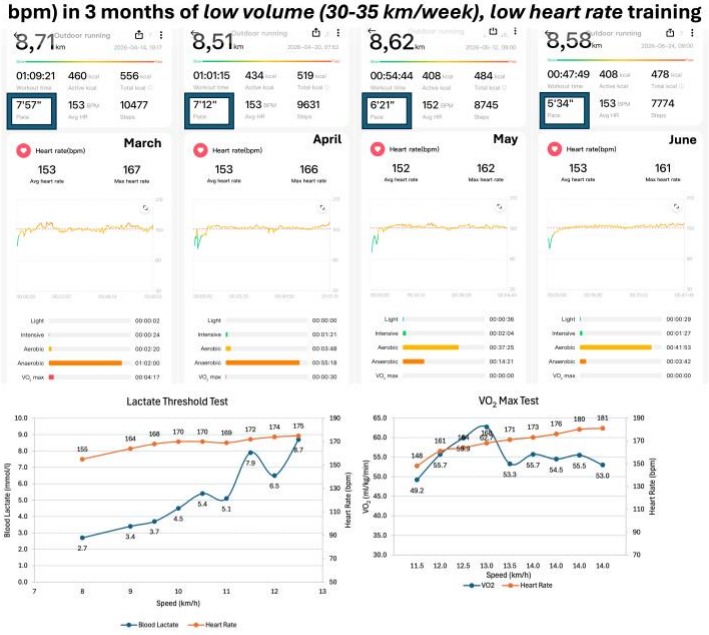
The GOLD-domain seven-transmembrane (GOST) protein family is relevant as an adjacent—not equivalent—architecture. GPR180, TMEM87A/B, GPR107/108, TMEM145, TMEM181, and WLS share a seven-transmembrane framework but do not generally behave as canonical G-protein-coupled receptors. GPR180 is especially informative: it has been linked to thermogenic adipocyte competence, lipid handling, and mitochondrial bioenergetic phenotype without demonstrated canonical G-protein coupling (Balazova et al., 2021; Balazova et al., 2026).

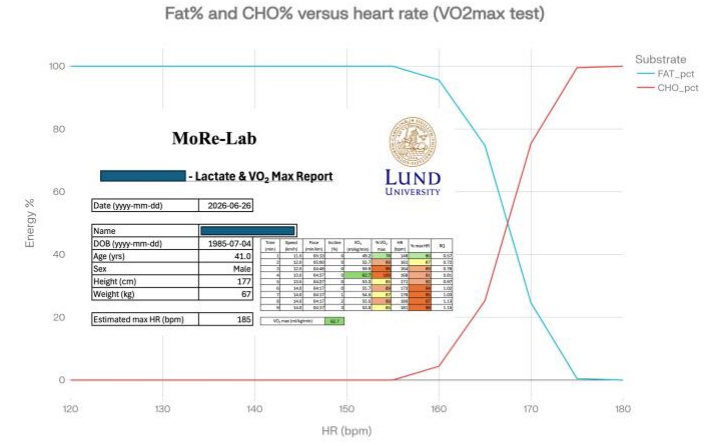
The lesson is not that GOST proteins are mitochondrial GPCRs. It is that eukaryotic cells appear repeatedly to recruit membrane-associated architectures to turn cellular context into organelle behavior. Canonical mGPCRs may specialize in rapid tuning of mitochondrial state. GOST-family members may more often influence slower programs of metabolic competence, trafficking, or organelle identity. The convergence is at the biological problem: context → organelle state.

7. Illustrative self-tracked observation: exercise adaptation as a state-transition phenotype

The participant is the author: a 41-year-old man with chronic post-traumatic trigeminal neuralgia and previous experience with prescribed cannabinoid-based therapy. During the observation period, the relevant biological transition was a change from sustained cannabinoid exposure associated with CB1 agonism to substantially reduced exposure. The purpose of documenting this transition is not to evaluate cannabis therapy, cannabinoid products, or dosing strategies, but to explore whether changes in a CB1-relevant signaling environment coincide with altered physiological adaptability following a standardized energetic challenge. The composite figure includes the reported progression, a laboratory lactate/VO_2 assessment, and substrate estimates. Importantly, the observation is presented because it represents the type of dynamic human phenotype predicted by the hypothesis: altered responsiveness to a physiological challenge following a change in regulatory state.

From VO2max 41 (fitness tracker) to 63 (lab VO_2 ≈ 63 ml/kg/min at 170 bpm) in 3 months of *low volume (30-35 km/week), low heart rate* training





As a 40-year-old with no endurance background, I followed a low-volume (30–35 km/week), low-heart-rate running protocol plus a proprietary ECS-supporting supplement stack. Over three months, my VO_2 capacity rose from a wearable-estimated 41 to a peak lab value of around 63 ml/kg/min at 170 bpm, LT1 and LT2 were set to 168 and 170 bpm, and my CHO/Fat profile showed that sub-155-bpm running is almost entirely fat-driven, while pushing harder than 170 bpm reduces running performance. Results documented in a university physiology lab test.

Figure 1. Illustrative self-tracked exercise and laboratory observation. The supplied composite figure reports a wearable-estimated VO_2max rise from 41 to approximately 63 mL·kg $^{-1}$·min $^{-1}$ over roughly three months of low-volume, low-heart-rate running, with a laboratory peak VO_2 near 63 mL·kg $^{-1}$·min $^{-1}$ at 170 bpm on 26 June 2026. The figure also presents a lactate threshold test, a substrate estimate showing near-complete fat oxidation below approximately 155 bpm, and tracker summaries of training distance and fitness. These are author-supplied, descriptive data. Wearable estimates are not equivalent to serial laboratory VO_2max testing; the laboratory endpoint does not validate the starting wearable value or establish mechanism.

The observation is compatible with several explanations. The default explanation remains conventional training adaptation, particularly given low initial fitness and the well-known capacity for large early gains. Other unmeasured contributors could include improved pacing, motivation, body mass, sleep, pain control, season, stress, diet, medication changes, measurement error, and regression to the mean. No direct measure of CB1 availability, endocannabinoid tone, muscle mitochondrial density, respiratory-chain function, or baseline laboratory VO_2 was obtained. The case therefore cannot establish a CB1, mtCB1, or mitochondrial explanation.

Its value is narrower: it suggests a phenotype worth testing. A similar energetic stimulus may not yield the same adaptation when the organism enters that stimulus in a different regulatory state. In the language of this paper, the candidate phenotype is reduced state-dependent metabolic receptivity: the capacity to receive a perturbation, make the appropriate mitochondrial transition, and consolidate adaptation during recovery. That is a research hypothesis, not a diagnostic category.

8. Testable predictions

- Validated mGPCRs should be enriched for ligands that convey energetically relevant context—nucleotide turnover, hypoxia, nutrient status, perfusion, circadian state, inflammation, neural activity, and survival signals—when compared with a prespecified non-olfactory GPCR background.
- Mitochondrial localization or receptor abundance should change during challenge. GPR35 provides proof-of-principle: ligand activation can drive trafficking to the outer mitochondrial membrane during ischemic stress (Wyant et al., 2022).
- Opposing receptor pairs should be common, because adaptive controllers require both recruitment and restraint. P2Y1/P2Y2 and AT1R/AT2R are candidate examples.
- Different mGPCRs should converge on a small number of mitochondrial hubs, measurable by complex activity, ATP-synthase organization, calcium uptake, cAMP, redox state, permeability transition, and recovery kinetics.
- Human relevance should be evaluated with dynamic outcomes, not resting biomarkers alone: substrate oxidation during graded exercise, repeat cardiopulmonary testing, running economy, heart-rate kinetics, recovery, and the change in these measures after standardized training challenges.

9. Limitations and translational boundaries

The mGPCR literature is real, but immature. Localization methods and functional depth vary; some entries in Table 1 remain preliminary. The proposed physiological “information” carried by a receptor is an inference from its known ligand system, not a direct demonstration that a mitochondrion reads that

information in vivo. Formal enrichment analysis has not yet been performed. The GOST comparison is conceptual and should not be used to expand the mGPCR census. These limitations are not peripheral—they define the next experiments.

For ECSre.store, scientific credibility depends on preserving this boundary. The framework should not be used to imply treatment efficacy, to make performance promises, or to advise changes in prescribed cannabinoid therapy. People using cannabis medically should discuss any dose changes with their treating clinician. This paper is designed to organize a research program around adaptive regulation, not to convert a plausible mechanism or an n=1 outcome into medical advice.

Conclusion

Mitochondria became indispensable not only because they make ATP, but because eukaryotic cells learned to govern their behavior. The mGPCR hypothesis proposes that a subset of host signaling systems participates in that governance by bringing physiological context directly to mitochondrial control nodes. The unifying idea is conditionality: mitochondrial output should be appropriate to the state in which it is produced, not simply maximal.

CB1 is a particularly compelling case because it connects a lipid-sensitive, state-dependent signaling system to complex-I-linked mitochondrial regulation. The broader receptor repertoire suggests that this is not an isolated curiosity. It may be one part of a distributed, host–organelle control layer that links nutrient state, energy turnover, perfusion, neural activity, circadian timing, stress, and survival to mitochondrial behavior. The consequence of impaired signaling may be less a failure of mitochondria at rest than a failure of adaptive range when conditions change. That proposition is specific enough to test—and restrained enough to be useful.

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Disclosure and data note

This is a hypothesis paper. The case observation concerns self-tracked data from the author; it is not a clinical trial, does not include third-party participants, and is not offered as evidence of efficacy for cannabinoid therapy or any intervention. Cannabinoid exposure history is reported only to define the biological transition being explored. No external funding was reported for the observation. The underlying wearable and laboratory materials are author-supplied.