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The neuro-metabolic epidemic and the CB1R paradox

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Obesity, metabolic syndrome, and neurodegenerative diseases are rising together, posing a public health issue. Alzheimer's disease, often referred to as "type-3 diabetes," shows how metabolic dysfunction can drive cognitive decline through disrupting brain insulin signaling, glucose metabolism, and causing inflammation. The endocannabinoid system, especially the CB1 receptor, plays a key role. While CB1R physiologically regulates energy homeostasis, chronic overnutrition leads to its pathological overactivation. Although CB1R antagonists showed strong efficacy in animal and early clinical studies, their development was halted due to neuropsychiatric side effects, underscoring an incomplete understanding of CB1R signaling across tissues and subcellular compartments. Incretin hormones, including GLP-1 and GIP, have emerged as key mediators linking metabolic control and brain health, exerting neuroprotective effects beyond glycemic regulation. Both the CB1R and incretin signaling converge on cyclic AMP pathways, suggesting that combined therapeutic strategies could improve metabolic and cognitive outcomes. Finding CB1R in mitochondria has changed our understanding, showing that cannabinoids can directly affect how cells produce energy by slowing complex I activity and interfering with how astrocytes and neurons share energy. This suggests that neuro-metabolic diseases are mainly problems with cell structures, not just with receptors.
This review brings together what is known about the CB1R paradox - the observation that this receptor, essential for normal energy homeostasis, becomes a pathological driver in conditions of chronic metabolic excess. We explore how incretins protect the brain, the critical role of mitochondrial CB1R, and how cell-type-specific CB1R signaling across neural and peripheral tissues drives both metabolic and cognitive pathology.

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The neuro-metabolic crisis: the "CB1R paradox" as a case study

The convergence of metabolic disorders and neurodegenerative disease represents a major challenge in modern medicine. Alzheimer's disease (AD) is increasingly conceptualized as "type-3 diabetes", reframing neurodegeneration as an early manifestation of systemic metabolic dysfunction rather than a late complication [1,2]. Emerging evidence shows that metabolic alterations at the mitochondrial level drive AD pathogenesis, linking impaired lipid metabolism and energy production in the brain to broader systemic dysfunction. These alterations reflect a "metabolic iceberg", where neurodegeneration represents the visible outcome of deeper bioenergetic failure [3–5]. Brain insulin resistance and impaired glucose metabolism preceded cognitive decline by years, often before classical neuropathology appears [2,6].

Obesity and metabolic syndrome contribute to brain dysfunction through central insulin resistance, reducing neuronal glucose uptake, impairing synaptic plasticity, and accelerating amyloid-β accumulation [7,8]. Type-2 diabetes (T2DM) increases AD risk by up to 2.5-fold [1,2,9,10].

Peripheral dysfunction promotes neurodegeneration via inflammation, oxidative stress, and mitochondrial impairment. Circulating cytokines activate microglia, while amyloid-related processes link pancreatic and brain pathology [2,7,10,11].

A unifying framework is the metabolic uncoupling between periphery and brain, where systemic insulin resistance and inflammation disrupt cerebral energy metabolism, driving neuroinflammation and cognitive decline [6,12–15].

Peripheral metabolic markers, including endocannabinoids (AEA, 2-AG) and adipokines, correlate with central dysfunction and may serve as early indicators of brain vulnerability [9,12–14]. However, most human evidence remains correlative.

The cannabinoid type-1 receptor (CB1R) exemplifies this neuro-metabolic tension. Under physiological conditions, the endocannabinoid system regulates energy balance, controlling feeding, lipid metabolism, and insulin sensitivity [14,16,17]. CB1R activity in the brain promotes food intake, while in peripheral tissues it modulates glucose and lipid homeostasis [14,18].

This system becomes pathological under chronic overnutrition. Chronic overnutrition disrupts this homeostatic system. Diet-induced obesity triggers persistent CB1R overactivation across central and peripheral tissues [19–21]. Persistent CB1R overactivation drives hyperphagia, leptin resistance, lipogenesis, insulin dysregulation, and gut barrier dysfunction [14,22]. In the hypothalamus, chronic CB1R activation impairs leptin signaling, promoting hyperphagia despite positive energy balance [23]. In the liver and adipose tissue, CB1R activation drives steatosis, lipogenesis, adipogenesis, and reduced energy expenditure, while in pancreatic β-cells and the intestine, it impairs glucose-stimulated insulin secretion, alters gut microbiota composition, and increases intestinal permeability, contributing to metabolic endotoxemia [14,16,24]. It also promotes inflammation and lipotoxicity through mediators such as resistin, establishing a feed-forward loop linking metabolic dysfunction and cognitive decline [13]. Understanding this paradox provides the overarching "why" for this review and illuminates the broader neuro-metabolic crisis.

Preclinical studies show that CB1R blockade improves weight, insulin sensitivity, hepatic steatosis, and cognition [22,25–28]. In sharp contrast to these robust preclinical outcomes [29,30], clinical translation failed due to neuropsychiatric adverse effects of centrally acting antagonists such as rimonabant [31] [14,22,32], highlighting the limitations of global receptor inhibition.

The CB1R paradox captures the central challenge: targeting pathological signaling while preserving physiological function. Current diagnostic paradigms still separate metabolic and cognitive assessments, limiting early intervention (Table 1).

This review integrates endocannabinoid signaling, incretin pathways, and mitochondrial dysfunction using CB1R as an organizing framework.

Cell-type specificity of CB1R: from plasma membrane to mitochondrial compartments

Neural cell specificity

Beyond the dichotomy between central and peripheral CB1R effects, emerging evidence reveals that CB1R expression and function vary across neural and glial cell types, contributing distinct roles to metabolism and cognition [33] In neurons, CB1R is concentrated at presynaptic terminals, where it suppresses neurotransmitter release via retrograde signaling, a mechanism essential for synaptic plasticity [34].

Astrocytes express high levels of CB1R and perform distinct metabolic functions [35]. CB1R regulates glucose uptake, lactate production, and metabolic support to neurons through the astrocyte-neuron lactate shuttle [36]. This function is essential for memory consolidation but becomes dysregulated in metabolic disease.

Cell-type specificity is critical, as global CB1R antagonism may block both beneficial and pathological signaling, contributing to adverse effects.

Subcellular compartmentalization: mitochondrial CB1R

CB1R function is further refined by subcellular localization. In addition to plasma membrane signaling, CB1R is present in mitochondria (mtCB1R), where it directly regulates cellular bioenergetics [34,35].

mtCB1R localizes to the outer mitochondrial membrane and modulates respiration via cAMP/PKA-dependent phosphorylation of Complex I, reducing ATP production [36,37]. In astrocytes, mtCB1R suppresses lactate production, limiting neuronal energy supply [36,37].

This compartmentalization explains why global CB1R antagonism produces both beneficial metabolic and adverse neuropsychiatric effects [38].

The solution is not to abandon CB1R as a therapeutic target, but to recognize that not all CB1R functions are pathological. Selective strategies—peripheral restriction, tissue specificity, or organelle targeting—may allow preservation of physiological signaling while inhibiting pathological pathways.

Incretins as neuro-metabolic integrators

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), the two primary incretin hormones, extend beyond glycemic control to function as neuro-metabolic integrators linking nutrient sensing, insulin secretion, and brain function [39–43].

GLP-1 and GIP are secreted by intestinal enteroendocrine L-cells and K-cells, respectively, in response to nutrient ingestion [44]. While their incretin effects are well-characterized in pancreatic β-cells, both peptides can cross the BBB and activate receptors expressed across brain regions implicated in cognition, affective

Table 1

Metabolic and neuropathological biomarkers: comparative analysis of CB1R blockade and incretin agonist strategies in the context of Neuro-Metabolic spectrum. This table summarizes the molecular reasons behind the idea that improving metabolism in the body, either by blocking CB1R or boosting incretin action, could help reduce brain problems and slow cognitive decline.

Biomarker/Parameter	Brain Vulnerability Link	CB1R Blockade Effects	Incretin Agonist Effects	References
Body weight	Obesity increases AD risk 1.5–2.5 fold	↓↓ in DIO models	↓↓↓ with GLP-1RAs and dual GLP-1/GIP agonists	[1,11]
Fasting glucose	Hyperglycemia promotes Aβ accumulation and oxidative stress in neurons	↓ in CB1R KO and antagonist-treated mice	↓↓ through enhanced insulin secretion and sensitivity	[1,2,6]
Glucose tolerance	Impaired glucose tolerance predicts cognitive decline independent of diabetes	↑↑ particularly in aged mice	↑↑↑ glucose-dependent insulin secretion)	[1,2,6,11]
HbA1c	↑ HbA1c correlates with hippocampal atrophy and memory deficits	Peripheral CB1R antagonism normalizes glycemic control	↓↓ sustained glycemic control	[1,6,11]
Insulin signaling	Peripheral insulin resistance mirrors brain insulin resistance; Hepatic insulin resistance increases systemic inflammation, affecting BBB integrity; Brain insulin resistance impairs memory formation, synaptic plasticity, and Aβ clearance and reduces neuronal glucose uptake	Indirect improvement via systemic metabolic correction: ↑↑ - restores insulin signaling in liver, muscle, adipose; ↑↑ particularly in aged skeletal muscle; ↑↑ - reduces hepatic steatosis and improves glucose production	↑↑↑ insulin sensitivity and enhanced glucose disposal; ↑↑ insulin-mediated glucose uptake; ↑↑↑ - reduces hepatic glucose production and steatosis; ↑↑↑ brain insulin signaling	[1,2,6,7,49]
Plasma triglycerides	Hypertriglyceridemia promotes BBB dysfunction and neuroinflammation	↓↓ - Peripheral CB1R blockade decreases lipogenesis	↓↓ through decreased lipogenesis	[14,22]
LDL cholesterol	Dyslipidemia accelerates Aβ deposition and vascular cognitive impairment	↓ - improved lipid profile in preclinical models	↓↓ - improved lipid metabolism	[14,22]
Hepatic steatosis	NAFLD is associated with cognitive decline	↓↓↓ - p53/miRNA-22/SIRT1/PPARα dependent	↓↓↓ in liver fat	[14,16]
Endocannabinoids (AEA and 2-AG)	↑↑ in obesity and correlate with central insulin resistance; Promote neuroinflammation and accelerate Aβ deposition; Impair brain glucose metabolism	↓ endocannabinoid tone; ↓↓ CB1R overactivation-induced insulin resistance and metabolic endotoxemia; Restoration of ECS-mediated energy homeostasis	↓ endocannabinoid signaling via enterolimbic axis modulation; OEA and PEA predict GLP-1RA metabolic efficacy and therapeutic response	[12–14,71]
Visceral Adiposity	Visceral fat releases adipokines, promoting neuroinflammation	↓↓ fat mass - peripheral CB1R in adipose tissue regulates storage	↓↓↓ through enhanced lipolysis	[9,14,24,25]
Leptin	Hyperleptinemia causes leptin resistance, impairing hippocampal synaptic plasticity	↓↓ leptin signaling, particularly with peripheral antagonists	↓↓ - weight loss normalizes adipokine signaling	[9,13,21,29]
GLP-1	Incretin dysfunction impairs glucose homeostasis and neuroprotective signaling	↑ incretin effects	Direct agonist effect through GLP-1RAs	[8,39–50,51–82]
GIP	GIP dysregulation affects insulin secretion and cognitive function	↑ GIP secretion	Direct agonist effect	[46,82]
Inflammatory markers	Peripheral inflammation drives microglial activation and synaptic loss	↓↓ - reduced adipose tissue inflammation	↓↓ - anti-inflammatory effects because modulating immune function	[7,13,14,61,62]
Oxidative stress markers	Systemic oxidative stress defeats brain antioxidant defenses	↓ through improved mitochondrial function	↓↓ through metabolic improvement and direct cellular effects	[11]
Mitochondrial function	Mitochondrial dysfunction disrupts astrocyte-neuron metabolic coupling	Unknown effect; mtCB1R activation reduces respiration; thus, its blockade may enhance respiration	↑ mitochondrial biogenesis and neuroprotection	[35–37,40,42,64,78]

(*continued on next page*)

Table 1. (*continued*)

Biomarker/Parameter	Brain Vulnerability Link	CB1R Blockade Effects	Incretin Agonist Effects	References
Brain glucose metabolism	Reduced cerebral glucose metabolism predicts AD progression	Indirect benefit through peripheral metabolic improvements	↑↑	[6,37]
Amyloid-β accumulation	Aβ oligomers disrupt synaptic function and insulin signaling	Unknown direct effect; peripheral benefits may reduce Aβ burden	↓↓ Aβ deposition in preclinical AD models	[1,2,11,61,62]
Tau Phosphorylation	Hyperphosphorylated tau disrupts axonal transport and neuronal viability	Preclinical evidence suggests a reduction through metabolic improvement	↓↓ tau hyperphosphorylation	[1,11,49]
Cognitive performance	/	Limited central effects with peripheral antagonists; Nootropic effect with CB1R inverse agonist	↑↑ cognition in early-phase trials	[50,64]
Depression/Anxiety scores	Metabolic dysfunction contributes to psychiatric comorbidities	↑↑↑ with global antagonists; peripheral CB1R selective antagonists are safer	↑↑ emotional well-being - antidepressant-like effects	[61,73]

Abbreviation: **AD**, Alzheimer's Disease; **Aβ**, Amyloid-beta; **BBB**, Blood–Brain Barrier; **CB1R**, Cannabinoid Receptor 1; **DIO**, Diet-Induced Obesity; **GIP**, Glucose-dependent Insulinotropic Polypeptide; **GLP-1RAs**, GLP-1 Receptor Agonists; **HbA1c**, Glycated Hemoglobin; **KO**, Knockout; **mtCB1R**, mitochondrial Cannabinoid Receptor 1; **ROS**, Reactive Oxygen Species; **T2DM**, Type 2 Diabetes Mellitus. **Symbols:** ↑, increase; ↓, decrease.

regulation, and energy homeostasis [39]. GLP-1 receptors (GLP-1R) are highly expressed in the hippocampus, frontal cortex, hypothalamus, and substantia nigra, areas critical for memory formation, executive function, energy homeostasis, and motor control [39,45]. Similarly, GIP receptors (GIPR) are present in hippocampal and hypothalamic circuits involved in cognition and feeding behavior [14,46].

At the mechanistic level, incretin signaling exerts pleiotropic neuroprotective effects. GLP-1R activation engages cAMP/PKA, PI3K/Akt, and MAPK pathways, collectively promoting neuronal survival, synaptic plasticity, mitochondrial integrity, and anti-apoptotic responses while dampening oxidative stress and neuroinflammation [39,47]. In experimental models of neurodegeneration, GLP-1R agonists (GLP-1RAs) reduce amyloid-β and tau pathology in AD, preserve dopaminergic neurons in Parkinson's disease, protect astrocytes and neural progenitors after ischemic stroke, and alleviate depressive behaviors [39,48]. Critically, GLP-1RAs restore brain insulin signaling and combat insulin resistance at the cellular level [49]. In palmitic acid-treated neurons, a model of lipotoxicity-induced insulin resistance, exendin-4 (Ex-4), a GLP-1RA, prevents mitochondrial dysfunction, suppresses reactive oxygen species (ROS) production, maintains insulin sensitivity, and enhances neurite outgrowth and dendritic spine morphogenesis [47]. These findings suggest that GLP-1RA administration may be beneficial for improving neuropathology in the metabolic-compromised brain characterized by lipotoxicity and metabolic inflexibility [47].

Moreover, GLP-1R has been implicated in the regulation of autophagy, remyelination, and microglial reprogramming toward anti-inflammatory states [39,50]. Dual GLP-1/GIP receptor agonists demonstrate even more potent effects [51]. Compounds such as DA-CH3 rescue spatial acquisition and memory impairments in APP/PS1 transgenic mice while attenuating excessive plaque deposition, gliosis, synaptic damage, endoplasmic reticulum stress, and derailed autophagy [50]. These effects reflect rectified Akt signaling and resolution of proteostasis machinery dysfunction, supporting the therapeutic rationale for GLP-1/GIP RA approaches [50].

Although the widespread expression of GIP receptors in the brain has been documented for nearly two decades [52], their functional relevance in physiological brain processes has only recently been clarified. GIP receptor signaling directly modulates hippocampal cognition, synaptic plasticity, and adult neurogenesis [45,53]. GIP analogues potentiate hippocampal long-term potentiation (LTP), while GIPR blockade impairs memory, supporting a causal role for endogenous GIP in cognition [46]. GIPR activation promotes neuronal progenitor proliferation in the dentate gyrus and exerts marked neuroprotective effects in neurodegeneration models, attenuating synaptic dysfunction and cognitive decline [53].

The clinical translation of incretin-based therapies in neurodegeneration is promising but remains incomplete [8]. GLP-1RAs, including liraglutide, exenatide, semaglutide, and dulaglutide, cross the BBB and have demonstrated acceptable safety profiles, along with signals of neuroprotective efficacy in early-phase clinical trials [39,41]. In patients with Parkinson's disease, GLP-1RA treatment has been associated with attenuation of cortical atrophy, preservation of cerebral glucose metabolism assessed by FDG-PET, and improvements in quality of life and motor function [39,54]. However, effects on canonical Alzheimer's disease biomarkers, such as Aβ42 and tau, have thus far been inconsistent, and translation into robust, reproducible cognitive benefits has varied across trials [39].

Importantly, accumulating phase II clinical evidence suggests that GLP-1RAs may exert disease-modifying effects rather than purely symptomatic benefits. Multiple randomized phase II trials have demonstrated that GLP-1 analogues, including exendin-4, liraglutide, and lixisenatide, significantly improve motor and cognitive outcomes in Parkinson's disease, with therapeutic effects persisting beyond treatment discontinuation [55–58]. Notably, liraglutide has also shown efficacy in slowing cognitive decline and reducing brain atrophy in a phase II Alzheimer's disease trial, providing the first clinical evidence that incretin-based therapies can alter disease trajectories in dementia [59]. Ongoing phase III trials evaluating exendin-4 in Parkinson's disease and semaglutide in Alzheimer's disease further underline the translational potential of this therapeutic strategy and position incretin-based drugs as leading candidates for disease modification in neurodegenerative disorders [55,60–62]. In contrast, clinical data for GIP-specific and dual GLP-1/GIP receptor agonists in neurodegeneration remain preliminary, with current human evidence largely confined to metabolic outcomes.

Despite robust preclinical success, CNS incretin signaling mechanisms are largely inferred from animal models rather than directly demonstrated in humans [63]. While FDG-PET can reveal glucose metabolism changes, the specific molecular cascades activated by GLP-1R and GIPR in human neurons remain poorly characterized [64]. Future studies combining advanced neuroimaging, CSF biomarker profiling, and iPSC-derived neural models are needed.

CB1R–incretin crosstalk: a rational foundation for combination therapies

The endocannabinoid system and incretin hormones represent two opposing yet intimately interconnected hormonal systems that converge on shared intracellular signaling pathways, particularly cAMP, to regulate metabolic homeostasis and CNS function [65–67]. This crosstalk provides a mechanistic rationale for combined therapeutic approaches targeting both systems [12,68] (Figure 1).

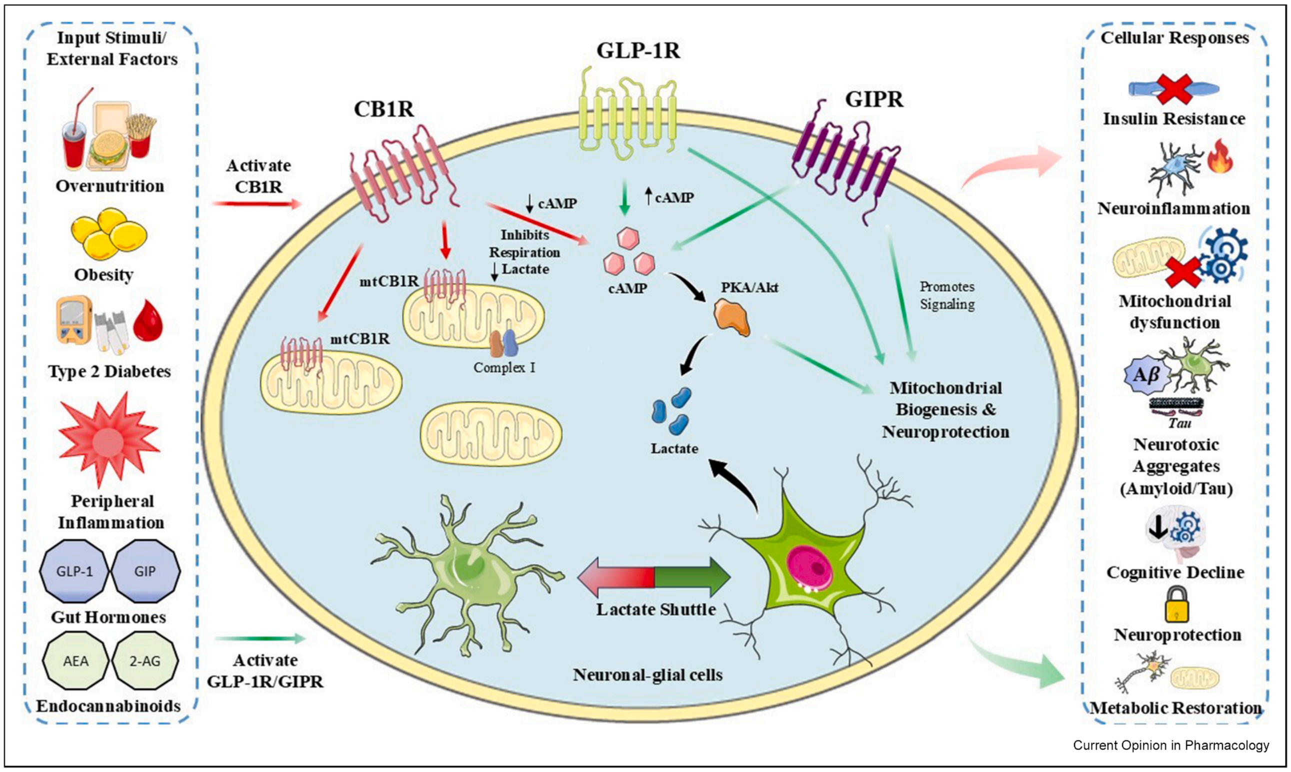
CB1R couples to Gi/o proteins and reduces cAMP, while GLP-1R and GIPR couple to Gs proteins and elevate cAMP [14,65,66,68]. In pancreatic β-cells, CB1R antagonism potentiates GLP-1-mediated insulin secretion by relieving cAMP inhibition [66]. CB1R inverse agonists enhance GLP-1R-mediated insulin secretion and improve glucose-stimulated insulin secretion and glycemic control [66,69].

Beyond β-cells, the ECS–incretin convergence extends to adipose tissue, the liver, and the brain. In adipocytes, CB1R blockade combined with GLP-1RA treatment produces additive effects on lipolysis, fatty acid oxidation, and mitochondrial biogenesis [12,67]. Animal models with genetic loss of CB1R or pharmacological blockade have shown restoration of mitochondrial biogenesis under high-fat diet conditions [70]. In neurons, both pathways modulate synaptic plasticity, with CB1R activation generally suppresses, while GLP-1R activation enhances synaptic plasticity and long-term potentiation (LTP) [39], mediated via downstream cAMP effectors including protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac), serve as downstream effectors mediating these opposing effects on neuronal excitability and survival [65].

Preclinical evidence supports the therapeutic potential of combined CB1R blockade and incretin agonism. OLHHA, a dual PPARα agonist and CB1 antagonist, combined with liraglutide produced superior metabolic outcomes in high-fat high-fructose diet-fed rats compared to either agent alone [12]. The combination therapy was most effective in promoting body weight loss and ameliorating both central and peripheral alterations, including restoration of hypothalamic proteins regulating food intake, the endocannabinoid system, the insulin pathway, and inflammation, while preventing tau hyperphosphorylation and neurodegenerative changes [12]. Similarly, studies using the peripherally restricted CB1R inhibitor JD-5037 in combination with long-acting GLP-1RA achieved greater reductions in body weight and fat mass than monotherapies, promoting negative energy balance in diet-induced obese mice [67]. This multitarget approach manages the multifactorial nature of obesity-associated neurodegeneration more comprehensively than single-agent therapy [12].

CB1R differentially regulates GLP-1 and GIP secretion through cell-specific mechanisms requiring further investigation [69,71].

Figure 1



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CB1R–Incretin Crosstalk: A Convergent Axis on cAMP and Bioenergetics. The incretin receptors GLP-1R and GIPR increase intracellular cAMP levels, promoting insulin secretion, mitochondrial function, and synaptic plasticity. The CB1R receptor exerts the opposite effect, inhibiting cAMP production. The balance between incretin signaling and endocannabinoid tone determines metabolic and cognitive outcomes and provides a rationale for combination therapies.

ECS-incretin crosstalk extends beyond peripheral metabolic control. CB1R activation tonically counters GLP-1 and GIP insulin secretagogue actions [69]. GLP-1 neurons in the nucleus tractus solitarius project throughout the CNS and regulate feeding, stress, and reward processing, influenced by peripheral endocannabinoids and gut-derived GLP-1 [72,73]. Endocannabinoid-related molecules predict the metabolic efficacy of GLP-1RA in humans with obesity [74].

Despite the convergence of CB1R and incretin signaling on cAMP and the compelling preclinical data supporting combination therapies [68], no clinical trials have yet evaluated combined CB1R antagonism and GLP-1RA effects on cognition in metabolic syndrome or early cognitive impairment.

Important questions include optimal timing, dosing, patient selection, and whether peripheral metabolic improvements translate into meaningful CNS outcomes. Future studies integrating advanced neuroimaging (FDG-PET, fMRI), CSF biomarker profiling (Aβ, tau, neuroinflammation), and iPSC-derived neuronal models are needed to clarify the therapeutic potential of ECS–incretin synergy in human brain health (Table 2).

Mitochondria bioenergetics as the convergent nexus

The intimate connection between mitochondrial dysfunction and both metabolic disease and neurodegeneration positions the mitochondrion as the critical nexus where systemic metabolic derangements converge to drive brain pathology [2,11,75,76]. Obesity and high-fat diets induce profound mitochondrial dysfunction in hypothalamic and hippocampal circuits, areas most susceptible to metabolic and cognitive decline [2,47,75].

The discovery of mtCB1R fundamentally altered our understanding of how CB1 receptors regulate distinct aspects of neuro-metabolic function. CB1R activation impairs mitochondrial function in hypothalamic circuits regulating energy homeostasis, contributing to leptin resistance [12,47,75].

However, a critical distinction emerges when examining cell-type specificity in mtCB1R overactivation: neuronal mtCB1R and astrocytic mtCB1R exert opposing yet complementary effects on brain bioenergetics.

In hypothalamic neurons, particularly pro-opiomelanocortin (POMC) neurons, a key population regulating energy balance, chronic mtCB1R overactivation primarily impairs neuronal ATP production and mitochondrial respiration [40]. By contrast, in astrocytes, mtCB1R overactivation has distinct metabolic consequences that are equally pathogenic but operate through a different mechanism: disruption of the astrocyte-neuron lactate shuttle [36,37].

Normal CB1R signaling preserves astrocyte-neuron lactate coupling, a process essential for memory consolidation and synaptic plasticity [36].

This lactate transfer from astrocytes to neurons is not merely supportive; it is obligatory for high-demand cognitive tasks including memory formation and long-term potentiation [42]. Pathological CB1R overactivation disrupts this coupling [36,42,65] and critically, this disruption can occur even under modest CB1R activation states that do not fully suppress neuronal mitochondrial respiration [2]. This dissociation has profound implications: it means that astrocytic mtCB1R dysfunction can impair cognition independently of gross neuronal bioenergetic collapse, suggesting that astrocytic lactate dynamics represent a particularly sensitive node in the CB1R-regulated neuro-metabolic network.

Why does this distinction matter therapeutically? Because the molecular targets controlling astrocytic lactate production differ from those governing neuronal respiration. Astrocytic mtCB1R operates through Gi-protein-dependent inhibition of soluble adenylyl cyclase (sAC) and reduction of cAMP-dependent phosphorylation of mitochondrial complex I subunits, particularly NDUFS4 [37,42]. This cascade reduces astrocytic oxygen consumption and, crucially, shifts metabolism toward glycolysis at the expense of oxidative lactate production [37]. Notably, GLP-1R activation simultaneously enhances astrocytic cAMP and mitochondrial biogenesis [45], directly opposing mtCB1R-mediated lactate suppression, a mechanistic convergence that preclinical studies now support and that may explain the cognitive benefits observed in GLP-1RA clinical trials.

Recent preclinical studies have provided complementary evidence supporting this astrocytic mechanism. Hebert-Chatelain et al. (2016) first demonstrated that genetic exclusion of CB1R from neuronal mitochondria prevented cannabinoid-induced memory impairment [77]. More recently, Fernández-Moncada et al. (2024) extended this paradigm to astrocytes, showing that astroglial mtCB1R activation suppresses lactate production and impairs novel object recognition memory [36]. Critically, these studies employed complementary methodologies that strengthen mechanistic inference: Hebert-Chatelain et al. (2016) used the DN22-CB1 mutant mouse to dissect neuronal mtCB1R function, while Fernández-Moncada et al. (2024) employed inducible astrocyte-specific CB1 deletion to isolate astrocytic effects. This methodological diversity, combining genetic gain-of-function and loss-of-function approaches with complementary conditional systems, substantially strengthens confidence in the astrocytic mechanism.

A notable gap remains, however: no study has simultaneously measured neuronal mtCB1R activity, astrocytic lactate production, and neuronal lactate uptake during cognitive tasks in the same animals. Such integrated, multi-compartmental measurements would be essential to prove causality and to determine whether the memory-impairing effects of CB1R activation are driven primarily by disrupted lactate coupling, impaired neuronal respiration, or a combination of both.

Despite revolutionary preclinical insights on mtCB1R [78], clinical data on mitochondrial ECS signaling in human disease are virtually absent. No studies have directly measured mtCB1R expression in human brain tissue from patients with metabolic syndrome or neurodegeneration. No mtCB1R-selective pharmacological tools are available for human use [79]. Bridging this gap requires PET tracers, postmortem tissue analysis, and development of subcellular-selective CB1R modulators.

Therapeutic strategies and future directions

The neuro-metabolic epidemic demands a fundamental reconceptualization of therapeutic strategy, moving beyond single-receptor pharmacology toward integrated, multi-target approaches that address the multifactorial interplay between peripheral metabolism, central bioenergetics, and neurodegeneration [9,15]. Three major therapeutic avenues have emerged, each with distinct mechanisms, benefits, and limitations, but all pointing toward a convergent future of organelle-centric neuro-metabolic pharmacology.

Peripherally restricted CB1R antagonists refined the rimonabant approach to retain metabolic benefits while avoiding neuropsychiatric toxicity. Compounds with limited BBB penetration ameliorate obesity, T2DM, and insulin resistance in animal models [80]. Novel peripherally restricted agents such as CRB-913 show improved safety profiles in preclinical trials [68]. Clinical development of several peripheral CB1R antagonists improves systemic metabolism through mechanisms

Table 2

Therapeutic Strategies Targeting the Endocannabinoid System and Incretin Pathways: Mechanisms, Efficacy, Neuroprotection Profile, and Clinical Development Status. This table brings together evidence that treating both metabolic problems in the body and brain, such as insulin resistance or inflammation, simultaneously is more effective at protecting the brain than single treatments. The table highlights the gap between promising lab results and real-world treatments, underscoring the need for long-term safety studies, methods to assess cognitive effects, and a better understanding of how the body and brain interact. The table compares treatments targeting the endocannabinoid system and incretin pathways for obesity, metabolic disorders, and cognitive decline. Each strategy is evaluated across some integrated dimensions: Primary Mechanism of Action; Metabolic Benefits; Neuroprotective Effects; Major Limitations; Clinical Development Stage.

Therapeutic Strategy	Primary Mechanism of Action	Metabolic Benefits	Neuroprotective Effects	Major Limitations	Clinical Development Stage	Supporting Evidence
Global CB1R antagonists	Reduces food intake, increases energy expenditure, inhibits hepatic/adipose lipogenesis	↓↓↓ Body weight, ↑↑ insulin sensitivity, ↓↓ hepatic steatosis, ↓↓ triglycerides, ↑ glucose tolerance	Unknown	↑↑↑ psychiatric adverse effects (depression, anxiety, suicidality ~26% patients)	Rimonabant: Withdrawn (2008) due to safety concerns	[13,14,22,27,28]
Peripherally restricted CB1R antagonists	Preserves central CB1R function while targeting metabolic tissues	↓↓ Body weight, ↑↑↑ insulin sensitivity (muscle, liver, adipose), ↓↓↓ hepatic steatosis, ↓↓ systemic inflammation, ↑ glucose homeostasis	Indirect through peripheral metabolic improvement; direct CNS effects are uncertain due to limited BBB penetration	Mechanistic uncertainty whether peripheral effects translate to neuroprotection; clinical trials ongoing	Phase I/II various candidates: JD-5037, AM6545, CRB-913, MRI-1891) promising early safety data	[27,28,67,68,71,84]
mtCB1R-selective modulators	Selective targeting of mitochondrial CB1R to enhance Complex I respiration and restore bioenergetics without affecting plasma membrane CB1R	Theoretical: ↑↑↑ cellular bioenergetics, ↑ mitochondrial respiration, improved metabolic flexibility (no clinical data)	Theoretical: ↑↑↑ neuronal bioenergetics, restored astrocyte-neuron metabolic coupling, ↓ oxidative stress (no clinical validation)	No mtCB1R-selective compounds exist; no PET tracers for in vivo imaging; complete absence of human clinical data; mechanistic tools lacking	Preclinical research only; no clinical-grade compounds available	[42,78]
GLP-1 receptor agonists	Increase insulin secretion (glucose-dependent), slow gastric emptying, promote satiety, enhance neuronal insulin signaling, cross the BBB	↓↓↓ Body weight, ↑↑↑ glycemic control, ↓↓ HbA1c, ↓↓ hepatic steatosis, ↓ cardiovascular risk	↑↑ Cerebral glucose metabolism (FDG-PET), ↑ brain insulin signaling, ↓ Aβ and tau pathology (preclinical), ↓ cortical atrophy, ↑ cognitive scores (early trials)	GI side effects (nausea, vomiting); cost; long-term safety data still accumulating; variable cognitive benefits in AD trials; effects measured by surrogate markers	FDA-approved for T2DM and obesity; Phase II/III trials for AD (EVOKE, EVOKE PLUS, ELAD trials ongoing)	[8,39,41,61,62,82]
Dual GLP-1/GIP agonists	Synergistic effects on insulin secretion, weight loss, and metabolic regulation	↓↓↓↓ Body weight (superior to GLP-1 alone), ↑↑↑↑ insulin sensitivity, ↓↓↓ HbA1c, improved lipid profile	↑↑ Neuroprotection (similar to GLP-1RAs), with potential synergistic benefits from dual incretin activation	Similar GI side effects to GLP-1RAs; higher cost; limited long-term data; neuroprotective effects are less studied than GLP-1 alone	FDA-approved (tirzepatide) for T2DM and obesity; early neuroprotection studies planned	[50,82]
Combined CB1R Blockade + GLP-1R agonism	CB1R blockade removes tonic cAMP inhibition, potentiating GLP-1-mediated insulin secretion, lipolysis, and mitochondrial biogenesis	↓↓↓↓ Body weight (greater than monotherapy); ↑↑↑ insulin sensitivity; ↓↓↓ hepatic steatosis; ↑↑ negative energy balance	↑↑↑ superior cognitive outcomes vs. monotherapy (preclinical); converges on insulin resistance, lipotoxicity, neuroinflammation, oxidative stress	Complexity of dual therapy; potential drug–drug interactions; optimal dosing ratios unclear; limited clinical data; cost considerations	Preclinical proof-of-concept; clinical trials needed	[1,2,6–9,13,14,22,27,28,39,47,50,73]

PPARα Agonist/CB1 antagonist dual ligands (OLHHA)	Dual PPARα agonism (improves lipid metabolism) and CB1 antagonism (reduces food intake, enhances energy expenditure)	↓↓ Body weight, ↓↓ hepatic steatosis, ↑ lipid oxidation, ↓ visceral adiposity	↓ Neuroinflammation; ↓ oxidative stress in the brain; improved tau expression (preclinical HFHFD model)	Preclinical stage only; human safety and efficacy unknown; optimal receptor selectivity ratios need refinement	Preclinical (OLHHA in rodent models)	[6,12]
Triple therapy: GLP-1 + PPARα/CB1 (OLHHA + LIG)	Multi-target approach: GLP-1R-mediated satiety/insulin sensitization + PPARα-enhanced fat oxidation + CB1 antagonism-reduced intake	↓↓↓ Body weight (most effective), normalized plasma parameters, ↓↓↓ hepatic steatosis, comprehensive metabolic correction	↑↑↑ most effective in normalizing brain protein expression, reversing HFHFD-induced neurodegeneration markers, improved insulin pathway	Multi-drug complexity; preclinical only; adherence challenges; cost; long-term safety unknown; requires extensive clinical validation	Preclinical (rat HFHFD models); demonstrated efficacy vs. monotherapies	[12]

Abbreviations: CB1R, Cannabinoid Receptor 1; **GLP-1**, Glucagon-like Peptide-1; **GLP-1R**, Glucagon-like Peptide-1 Receptor; **HFHFD**, High-Fat High-Fructose Diet; **LIG**, Liraglutide; **mtCB1R**, mitochondrial Cannabinoid Receptor 1; **OLHHA**, N-oleoyl-homoserine-hydroxy-alpha-lactone (a dual PPARα agonist/CB1 antagonist); **PPARα**, Peroxisome Proliferator-Activated Receptor alpha; **T2DM**, Type 2 Diabetes Mellitus. **Symbols:** ↑, increase; ↓, decrease.

largely independent of appetite suppression [81], though whether benefits translate into direct neuroprotection remains uncertain [22].

GLP-1RAs and dual GLP-1/GIP agonists have revolutionized the treatment of obesity and T2DM, producing unprecedented weight loss (up to 15–20% with tirzepatide and semaglutide) and robust glycemic control [73,82]. The novel CB1R inverse agonist CRB-913 demonstrates additive effects when combined with incretin analogs, resulting in 32.6%, 28.8%, and 16.8% decreases in body weight when combined with tirzepatide, semaglutide, and liraglutide respectively [68]. Beyond their established metabolic actions, these agents exert pleiotropic effects with neuro-mitochondrial relevance. GLP-1RAs increase adiponectin secretion, suppress inflammatory tone, improve endothelial function, and modulate hepatic lipid metabolism [9,67]. GLP-1 analogs demonstrate efficacy beyond traditional diabetes applications, including neuroprotective effects in Parkinson's disease, as evidenced by improved motor scores and emotional well-being, as well as benefits in Alzheimer's disease by improving brain glucose metabolism and glucose transport across the blood–brain barrier [41]. At the cellular level, they enhance mitochondrial biogenesis, improve respiratory capacity, and reduce oxidative stress [39,47]. In the brain, they activate neuroprotective signaling cascades, reduce neuroinflammation, and preserve synaptic function [39,41]. The dual incretin analog DA-CH3 rescues spatial acquisition and memory impairments in APPSWE/PS1E9 mice, attenuating excessive plaque deposition, gliosis, and synaptic damage by resolving endoplasmic reticulum stress and derailed autophagy [50]. However, their neuro-mitochondrial actions remain underexplored in human studies, with clinical evidence limited primarily to surrogate markers (e.g., glucose metabolism on FDG-PET) rather than direct measures of mitochondrial function [39].

The rationale for combination therapies targeting ECS, incretins, and mitochondrial function is compelling. Preclinical studies demonstrate that combined peripheral CB1R antagonism and GLP-1RA treatment produces superior metabolic and cognitive outcomes compared to either agent alone [12]. The mechanistic synergy is clear: CB1R blockade removes tonic inhibition of cAMP, thereby potentiating GLP-1-mediated insulin secretion, lipolysis, and mitochondrial biogenesis [12,66]. Furthermore, both interventions converge on common pathological nodes, insulin resistance, lipotoxicity, neuroinflammation, oxidative stress, providing multiple points of therapeutic leverage [12,67].

Future therapeutic priorities must focus on several critical frontiers: first, development of mtCB1R-selective modulators could preserve beneficial CB1R functions while targeting pathological mitochondrial signaling [83]. Recent structural studies on peripherally restricted CB1R antagonists reveal they maintain high-affinity binding with reduced brain penetration [84], suggesting that chemical strategies including mitochondria-targeting moieties could enable selective mtCB1R modulation [42]; second, integration of mitochondrial fitness as a therapeutic endpoint would fundamentally shift clinical trial design. Rather than relying solely on gross measures of cognition (MMSE, ADAS-Cog), trials should incorporate direct assessments of mitochondrial function biomarkers [6,85]. These biomarkers would enable patient stratification, dose optimization, and mechanistic confirmation of target engagement; third, endocannabinoid biomarkers (2-AG, AEA, OEA, PEA) and incretin receptor PET imaging could stratify responders to combination therapy [13,14,39,74]. Integration of metabolomic, lipidomic, and proteomic profiling would enable construction of multi-omic signatures predicting therapeutic response; fourth, human induced pluripotent stem cell (iPSC)-derived neural models and the enterolimbic axis framework will bridge preclinical findings to human neuro-metabolic disease [42,72,73].

Resolving the CB1R paradox - why a receptor system essential for energy homeostasis becomes pathogenic in metabolic disease - requires abandoning receptor-centric pharmacology in favor of organelle-centric approaches. The discovery that CB1R exerts distinct functions when localized to plasma membranes versus mitochondria fundamentally reshapes our conception of cannabinoid signaling and opens unprecedented therapeutic opportunities. By selectively targeting mtCB1R in astrocytes to restore lactate production, or in neurons to enhance Complex I function, we could address the bioenergetic crisis at the heart of neuro-metabolic disease without the neuropsychiatric liabilities of global CB1R antagonism. Combined with peripherally restricted CB1R antagonists to improve systemic metabolism and incretin-based therapies to enhance insulin signaling and mitochondrial biogenesis, this multi-pronged strategy offers the most promising path forward. The neuro-metabolic epidemic is fundamentally a crisis of cellular energy metabolism, mitochondrial dysfunction in neurons and astrocytes starved of fuel by peripheral insulin resistance and dysregulated endocannabinoid tone. Only by targeting this bioenergetic nexus at the subcellular level can we hope to prevent, halt, or reverse the inexorable progression from metabolic syndrome to cognitive decline.

Credit authorship contribution statement

Francesca Vaccaro: Writing – review & editing. Ginevra Malta: Writing – review & editing. Manfredi Rizzo: Writing – review & editing. Fulvio Plescia: Writing – review & editing, Writing original draft, Conceptualization. Gianluca Lavanco. Writing – review & editing, Writing original draft, Conceptualization. All the authors read and approved the final manuscript.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used Grammarly in order to improve the readability and language. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the published article.

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** of outstanding interest

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