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Glucocorticoid receptor alpha as a core survival receptor: mechanisms, and implications for health and critical illness

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Abstract

The glucocorticoid receptor alpha (GRα) is traditionally viewed as a stress-response element with anti-inflammatory properties. Mechanistically, convergent evidence from global and tissue-specific knockout models, translational clinical studies, and evolutionary analyses indicates that GRα's vital role in maintaining systemic homeostasis challenges its peripheral classification in clinical medicine. To reconceptualize GRα as a master regulator of organismal survival by analyzing its non-redundant, multisystemic functions and evaluating its relevance in health, development, and critical illness. This narrative synthesis combines structured searches performed using the Consensus AI research platform with evidence from genetic knockout models, tissue-specific deletion studies, and translational clinical research. Key findings are framed within comparative receptor analyses and integrated into broader physiological models of homeostasis and allostasis. Evolutionarily, global loss of GRα is perinatally lethal, characterized by failure of lung maturation and respiratory adaptation, accompanied by metabolic and neuroendocrine dysregulation. Tissue-specific deletions reveal essential roles in immune regulation, mitochondrial bioenergetics, cardiovascular function, and neuroendocrine stability. While several other receptors (including MR) are also essential for survival, GRα is distinctive for the breadth of cross-system coordination it provides. GRα exhibits both genomic and non-genomic actions that support rapid stress adaptation and promote restoration of systemic stability. Clinically, despite this broad integrative role, GRα's survival-critical functions remain underrecognized in therapeutic strategies. Overall, the evidence supports GRα as a central integrator of postnatal survival, metabolic resilience, and immunological competence. GRα is a vital receptor whose systemic regulatory functions exceed its historical classification as a stress hormone mediator. Its role is not ancillary but foundational, anchoring survival across immune, metabolic, cardiovascular, and neuroendocrine systems. The collapse of this receptor's function is not simply a component of disease—it is the tipping point that drives the organism from adaptation toward systemic breakdown. Recognizing GRα as a master survival receptor redefines therapeutic priorities, guiding biomarker-driven restoration of homeostasis in critical illness.

Keywords

glucocorticoid receptor alpha (GRα), mineralocorticoid receptor (MR), stress adaptation, receptor essentiality, postnatal survival, glucocorticoid resistance

Introduction

Homeostasis and glucocorticoid receptor alpha (GRα) as central axes of survival

The concept of homeostasis—the intrinsic ability of biological systems to maintain stable internal conditions despite continuous external and internal perturbations—remains the cornerstone of physiology. Originally conceptualized by Claude Bernard and later formalized by Walter Cannon [1], this principle captured the adaptive constancy of internal environments in the face of change. Building upon this foundation, Hans Selye [2] expanded the concept through his theory of "general adaptation syndrome," highlighting the organism's organized multi-stage response to stress as a vital survival mechanism. Decades later, Sterling and Eyer [3] introduced the concept of "allostasis," describing predictive regulation in which the brain anticipates and prepares for physiological demands in advance to maintain stability through change. More recently, Sterling [4] clarified that effective regulation relies on the brain's ability to predict and proactively manage internal needs.

Expanding this framework, George E. Billman [5] reframed homeostasis not as a static endpoint but as a dynamic, integrative process controlled by flexible, multi-system adjustments that respond to both internal and external demands over time. Billman [5] emphasized that it is the breakdown of homeostatic regulation, rather than the underlying disease process itself, that ultimately leads to death. This perspective underscores that life depends more on the capacity for physiological coordination than on the elimination of pathology. Although Billman [5] did not specifically examine critical illness, his assertion that organismal death results primarily from homeostatic failure parallels the systemic breakdown seen in critically ill patients.

In line with this perspective, the present work proposes that GRα functions as a central regulator of homeostasis, coordinating metabolic, immune, neural, and vascular responses through both genomic and non-genomic pathways. Unlike many human receptors whose loss can be compensated for by redundancy, GRα performs an irreplaceable, life-sustaining role. Experimental deletion causes perinatal death from failed pulmonary adaptation and profound metabolic, immune, and neuroendocrine imbalances. Despite its evolutionarily conserved role and molecular indispensability, GRα remains underappreciated in clinical medicine as a survival receptor.

Modern therapeutic approaches still view glucocorticoids primarily as anti-inflammatory agents, overlooking their deeper purpose: to restore and preserve homeostasis during physiological stress. This narrow perspective persists despite extensive translational research demonstrating that activation of GRα is vital for postnatal survival and systemic integration [6]. The failure to translate this biology into clinical strategies has contributed to the ongoing marginalization of a receptor essential for life. Reframing GRα from a peripheral stress modulator to a central integrator of survival physiology is not merely conceptual—it is a clinical necessity.

By positioning GRα within the continuum of homeostatic regulation—first outlined by Cannon, expanded by Selye, and modernized by Billman—this manuscript proposes a unifying view: postnatal survival ultimately depends on sustained systemic homeostasis mediated by GRα. This reconceptualization invites a shift in clinical focus—from disease-centered interventions to strategies aimed at maintaining or restoring physiologic equilibrium—placing GRα at the core of adaptive survival.

Central scientific questions guiding this work

This manuscript investigates what makes GRα a vital receptor for survival.

The first question examines GRα's essential role after birth. The regulatory function of GRα in male and female fertility, fetal development, and postnatal maturation is thoroughly reviewed. Unlike most nuclear receptors (NRs), which often display partial overlap or functional redundancy, complete genetic deletion of GRα results in perinatal death due to multisystem failure, highlighting its unique and indispensable role in supporting life [6]. This contrasts sharply with deficiencies in receptors such as the mineralocorticoid receptor (MR), where loss of function produces more localized physiological disturbances largely attributable to electrolyte imbalance.

The second question explores why the loss of GRα leads to systemic collapse. Experimental and clinical evidence show that GRα acts as a master regulator, coordinating all organ systems and their systemic connections—including immune, metabolic, bioenergetic, cardiovascular, lymphatic, and neuroendocrine networks—to sustain organismal stability and homeostasis equilibrium [6]. In addition, GRα functions as a systemic integrator whose regulatory scope far exceeds that of typical tissue-restricted NRs. Its deletion disrupts mitochondrial activity, endothelial stability, neuroendocrine control, metabolic regulation, and coordinated inflammatory signaling—explaining why GRα absence produces global collapse rather than the organ-specific dysfunction seen with MR deficiency.

The third question investigates whether traditional models of stress and homeostasis adequately capture GRα's essential functions. The findings indicate that GRα goes beyond stress adaptation, serving as a fundamental regulator of homeostasis in both normal and stressful conditions. However, foundational frameworks—from Bernard and Cannon's formulation of homeostasis [1] to Selye's general adaptation syndrome [2], to Sterling and Eyer's model of allostasis [3], and Sterling's later clarifications on predictive regulation [4]—do not fully encompass GRα's organism-wide homeostatic role.

The fourth question examines whether GRα can serve as a unifying factor across both historical and modern theories of physiological regulation. By synthesizing the ideas of Bernard, Cannon, Selye, Sterling, and George E. Billman, GRα is regarded as a key component in the development of survival physiology. Billman's dynamic model of homeostatic regulation [5], when integrated with classical and contemporary perspectives, further positions GRα as a central mechanistic link connecting homeostasis, allostasis, and systemic stress adaptation. Despite this, GRα's central survival role has remained underrecognized, even in conditions marked by corticosteroid resistance, inflammation, and multisystem failure.

The final question considers translational implications: Could identifying GRα as a survival-critical receptor reframe therapeutic approaches from predominantly symptom management to actively restoring systemic homeostasis, especially in cases of critical illness and chronic conditions? Recognizing GRα as indispensable suggests clinical strategies aimed at restoring GRα signaling may improve outcomes in sepsis, acute respiratory distress syndrome (ARDS), autoimmune disease, neurodegeneration, and other conditions characterized by impaired GRα function.

In conclusion, this work supports redefining GRα as a key coordinator of homeostatic regulation and postnatal survival, with significant implications for both biological understanding and clinical practice.

Preface: receptor essentiality and GRα as a survival axis

Receptors in survival physiology

The human body contains hundreds of receptor systems that detect external and internal stimuli, regulate cellular signaling, and coordinate organ function. While most receptors function within overlapping or redundant networks that allow for partial compensation when one component fails, a small subset is essential for postnatal survival. These survival-critical receptors act as molecular sentinels and integrators, translating environmental and physiological cues into coordinated cellular and systemic responses.

Among them, the GRα and, to a lesser extent, the MR stand out as non-redundant survival regulators. In clinical terms, dysfunction of GRα is not just another molecular defect—it causes rapid deterioration across multiple systems, which is directly relevant to managing critical illness, shock, and severe systemic inflammatory conditions. Complete genetic deletion or sustained pharmacologic blockade of either receptor leads to early postnatal death, highlighting their unique, non-redundant roles in maintaining physiological function stability [7, 8].

Methodological overview

To explore these questions, targeted scientific inquiries were posed using Consensus, an AI-powered research synthesis platform. This structured method enabled an investigation into GRα's necessity across developmental stages, its role in maintaining organ function under both physiological and pathological stress, and its involvement in sustaining systemic homeostatic corrections during critical illness. The emphasis was on translational relevance—linking molecular and physiological findings to clinical strategies aimed at preserving or reactivating GRα signaling in high-mortality conditions. Evidence was drawn from global gene knockout models, tissue-specific deletion studies, and translational clinical studies collectively evaluating whether GRα is indispensable for postnatal survival and adaptation to environmental stress.

Evolutionary context and adaptive expansion

Comparative analyses suggest that the GRα-centered regulatory axis, which includes the hypothalamic-pituitary-adrenal (HPA) axis, Keap1-Nrf2 oxidative-stress sensors, and aquaporin-mediated water channels, evolved as an integrated survival network enabling immune resilience, oxidative protection, and fluid balance during the transition to terrestrial life. The HPA axis regulates stress-induced glucocorticoid release, the Keap1-Nrf2 pathway detects and neutralizes oxidative injury, and aquaporins conserve water to maintain hydration. These same regulatory pathways fail in advanced critical illness, explaining why GRα dysfunction leads to uncontrolled oxidative injury, capillary leakage, and inflammatory cascades.

Although direct evidence of GRα's non-redundancy during early vertebrate evolution is limited, studies of limb biomechanics suggest that systemic integrators, such as GRα, became more essential as vertebrates adapted to land, coordinating limb propulsion, neural input, and metabolic support [9]. From this perspective, critical illness reflects a state of functional GRα deficiency rather than receptor overactivation. The resulting phenotype of multi-organ failure arises when the GRα-centered network can no longer maintain mitochondrial energy production, immune regulation, and vascular integrity.

GRα's multisystem functions in health and development

GRα holds a central and evolutionarily conserved role in systemic homeostasis [10]. Though classically associated with the stress response, it regulates metabolism, immune function, cardiovascular and neuroendocrine integration, neural excitability, mitochondrial dynamics, epithelial and endothelial barrier function, lymphatic flow, and fluid balance. These effects arise from both genomic (nuclear gene regulation) and non-genomic (rapid extranuclear signaling) mechanisms, positioning GRα as a dominant regulator of dynamic, phase-specific physiological responses. When GRα signaling is disrupted, such as in septic shock or ARDS, instability across multiple systems explains why glucocorticoid therapy fails unless GRα signaling is restored to re-establish systemic homeostasis. Its importance lies not in a single dominant pathway, but it results in the integration and coordination of multiple organ systems and regulatory networks. Its regulation is further influenced by 11β-HSD1/2-dependent cortisol availability and by alternative GR isoforms (β and γ), which contribute to variation in homeostatic responses.

Oxidative/nitrosative stress, along with ICU-level micronutrient deficiencies, further compromises GR signaling. Redox injury reduces HDAC2 activity and promotes JNK/MAPK-mediated phosphorylation of GRα, leading to impaired nuclear translocation and accelerated nuclear export. Low levels of vitamin D, thiamine, selenium, and zinc weaken anti-inflammatory gene regulation, mitochondrial redox balance, and the NADPH-dependent 11β-HSD1 "local cortisol" regenerating system. Collectively, these factors diminish GRα signaling capacity across the endothelium, immune cells, liver, and brain, constituting functional impairment rather than loss of the receptor itself.

Mitochondrial maturation and postnatal transition

GRα is essential for neurodevelopment, immune system maturation, and metabolic adaptation during the perinatal window. Localizes not only in the nucleus but also in the mitochondria, GRα drives the metabolic switch from glycolysis to fatty acid oxidation, sustaining oxidative phosphorylation and ATP generation [11, 12]. Within mitochondria, GRα primarily functions in monomeric form, binding to glucocorticoid response element (GRE)-like regions in mitochondrial DNA, and interacting with mitochondrial transcription factor A (TFAM), which orchestrates mtDNA replication and transcription [13]. This interaction enhances energy production and limits oxidative stress, ensuring cellular adaptation. In fetal cardiomyocytes, GRα stimulates fatty acid oxidation to meet ATP demands of postnatal life. This similar metabolic shift is mirrored during recovery from critical illness, where mitochondrial GRα activation may determine whether patients regain organ function.

However, excessive or prolonged GRα activation can become maladaptive. Choi and Han [14] showed that chronic GR upregulation in cancer models impairs oxidative metabolism via transcriptional misregulation. Lapp et al. [15] showed that acute or low-to-moderate glucocorticoid exposure enhances mitochondrial oxidative capacity, whereas chronic or high-dose exposure suppresses it. This biphasic, dose- and context-dependent behavior suggests that GRα activation is restorative during acute stress, yet detrimental when prolonged, leading to oxidative exhaustion and metabolic collapse.

Comparative receptor roles: GRα vs. MR

GRα has undergone adaptive refinement to handle complex stress and immune challenges in terrestrial species. While MR shares overlapping roles—particularly in electrolyte balance and immune modulation—its loss results in localized dysfunction, such as macrophage impairment and vascular instability [7, 8, 16, 17]. In contrast, GRα deletion precipitates multisystem collapse involving neural, immune, and metabolic disintegration. This distinction has practical implications: MR-targeted therapies may correct localized disturbances, but only GRα restoration reverses global metabolic-immune-neuroendocrine collapse. Comparative studies in fish and mammals indicate that GRα's regulatory role expanded with terrestrial adaptation, supporting its classification as a system-critical receptor [10, 18].

Mechanistically, GRα engages a wide range of cofactors (CBP/p300, SRC-1, GRIP1) and interacts directly with transcription factors such as nuclear factor kappa B (NF-κB), AP-1, and peroxisome proliferator-activated receptor alpha (PPARα), enabling cross-system genomic coordination. Its non-genomic and mitochondrial signaling also supports kinase (PI3K/Akt, MAPK) activation and bioenergetic regulation—mechanisms largely absent in MR. These features confer on GRα a unique system-integrating capacity, whereas MR functions mainly within epithelial and vascular domains [19].

GRα: a neglected survival regulator in clinical medicine

Despite its essential role, GRα remains largely underrecognized in modern therapeutics. Table 1 outlines its functions across organ systems [6, 19–49], underscoring that GRα is not merely a molecular stress responder but the coordinating hub for multi-organ stability.

Table 1. Systemic functions of glucocorticoid receptor alpha (GRα) across major organ systems.

Organ/System	GRα function summary
Immune system	Coordinates resolution of inflammation by suppressing NF-κB/AP-1 cytokines, upregulating GILZ/MKP-1/Annexin A1, limiting neutrophil/macrophage survival, and supporting Treg-mediated tolerance [20–22].
Central nervous system	Modulates synaptic plasticity, hippocampal neurogenesis, and stress adaptation; provides negative feedback on the HPA axis to control glucocorticoid levels; influences emotional regulation via MR/serotonin signaling [28].
Peripheral nervous system	Influences autonomic outflow and neuroimmune crosstalk; regulates inflammatory tone and contributes to sensory and metabolic homeostasis under stress [23, 24].
Endocrine system	Controls HPA axis reactivity and feedback; modulates thyroid, gonadal, and growth hormone axes; coordinates stress hormonal signaling across endocrine networks [6, 25].
Cardiovascular and endothelium	Upregulates adrenergic receptors, enhances catecholamine sensitivity and NO production via eNOS; maintains vascular tone, limits inflammation and permeability; regulates sodium-fluid balance [19, 26–32].
Lungs	Suppresses airway inflammation, enhances β2-adrenergic bronchodilation, promotes alveolar repair and surfactant production, reduces vascular leakage in ARDS [33].
Kidneys	Promotes AQP2/ENaC expression to retain sodium/water; limits oxidative stress and inflammation; supports podocyte and epithelial structure under systemic stress [34–36].

Table 1. Systemic functions of glucocorticoid receptor alpha (GRα) across major organ systems. (*continued*)

Organ/System	GRα function summary
Liver	Regulates gluconeogenesis, lipid metabolism, acute-phase proteins; modulates inflammation and circadian-metabolic adaptation; ensures substrate mobilization [6, 37].
Gastrointestinal tract	Enhances barrier integrity via tight junction regulation; modulates gut microbiota composition; and reduces oxidative stress and systemic inflammation via gut immune signaling [6, 38–40].
Pancreas	Regulates insulin/glucagon secretion, controls 11β-HSD1 expression in islets; maintains glucose homeostasis; modulates circadian gene expression in β-cells [41–43].
Adipose tissue	Promotes lipolysis, modulates insulin sensitivity, limits inflammation; preserves mitochondrial function, and regulates adipokines under metabolic stress [44–46].
Muscle	Facilitates protein catabolism during stress adaptation, preserves mitochondrial integrity and glucose metabolism, and regulates oxidative stress and energy utilization [47–49].

This table summarizes the systemic functions of GRα across major organ systems, highlighting its integrative role in coordinating physiological stress responses. For a comprehensive recent review, which includes GRα regulation of circulating cells, see [6]. NF-κB: nuclear factor kappa B; AP-1: activator protein-1; GILZ: glucocorticoid-induced leucine zipper; HPA: hypothalamic-pituitary-adrenal; MR: mineralocorticoid receptor; NO: nitric oxide; eNOS: endothelial nitric oxide synthase; ARDS: acute respiratory distress syndrome; AQP: aquaporin; ENaC: epithelial sodium channel.

Disruption of GRα signaling underlies a spectrum of diseases. In critical illness (e.g., sepsis, ARDS), GRα resistance limits glucocorticoid efficacy, impairing control of inflammation, maintenance of vascular tone, mitochondrial energy output, and hemodynamic stability, all of which are essential for survival in critically ill patients [50, 51]. In chronic disorders—including autoimmune disease, inflammatory bowel disease, rheumatoid arthritis, chronic obstructive pulmonary disease, and major depressive disorder—dysfunctional GRα signaling drives persistent systemic imbalance [19, 52–57], perpetuating disease progression.

Yet, current frameworks focus narrowly on GRα's anti-inflammatory properties, neglecting GRα's broader integrative role. This limited view provides symptomatic relief without restoring the systemic coordination required for complete recovery. Therapeutic strategies that instead aim to restore and optimize GRα signaling could transform outcomes in critical care, improving survival, reducing life-support dependency, and accelerating recovery [6, 58].

GRα as a master survival receptor: clinical and physiological reframing

Given the breadth of its systemic influence, GRα must be reframed not as a peripheral stress responder, but as the principal regulator within an integrated survival axis—indispensable for maintaining multisystem stability under both basal and stress conditions. This clinical reframing bridges molecular physiology with patient outcomes, redefining therapeutic priorities across inflammatory, metabolic, neurodegenerative, and critical illness contexts.

While the MR also contributes to corticosteroid signaling, its functions remain domain-specific, such as the regulation of macrophage survival, vascular tone, and epithelial barrier integrity. Loss of MR leads to localized dysfunction, whereas loss of GRα triggers organism-wide collapse characterized by neuronal apoptosis, immune dysregulation, cardiovascular decompensation, mitochondrial failure, neuroendocrine instability, and impaired tissue repair and metabolic adaptation [7, 59]. GRα loss destabilizes the HPA axis [53], impairs mitochondrial bioenergetics [19], and disrupts the transcriptional programs essential for electrolyte balance, inflammation resolution, metabolic adaptation, and tissue restoration [60]. Clinically, this manifests as simultaneous hyperinflammation and immune paralysis, loss of vascular tone, metabolic failure—all hallmarks of poor outcome in critical illness [61]. The resulting multi-organ dysfunction underscores GRα's central role as the guardian of integrated homeostasis [61].

In conclusion, reframing GRα as a survival-critical receptor requires medicine to move beyond reductionist models toward systems-based strategies that preserve, enhance, and restore its signaling capacity. Because GRα loss precipitates a cascade of immune, metabolic, vascular, and neuroendocrine failures, its restoration must be recognized as a universal therapeutic goal wherever systemic dysregulation threatens survival. Evidence indicates re-establishing GRα function accelerates inflammation resolution, reduces vasopressor dependency, shortens ventilation duration, and improves survival—firmly establishing its translational importance as a master survival receptor [6, 58, 62].

This recognition sets the stage for Diversity and specialization of human receptors, which examines the molecular architecture and regulatory networks through which GRα sustains physiological stability—beginning with the diversity and specialization of human receptors, to place GRα's unique survival role within its broader biological context.

Diversity and specialization of human receptors

Human physiology relies on a vast and highly specialized repertoire of cellular receptors (Table 2) [63–87]. These receptors are broadly classified into membrane-bound, cytoplasmic, and nuclear families, each with distinct structural features and signal transduction mechanisms. Collectively, they orchestrate the detection and processing of extracellular and intracellular cues, regulate communication across tissues and organ systems, and coordinate the integrated physiological responses required for homeostasis, adaptation, and survival.

Table 2. Major human receptor families: types and functions.

Receptor family [primary location]	Number of types/Subtypes	Primary function	Survival-critical?	Loss consequences	Redundancy level
G protein-coupled receptors (GPCRs) [cell membranes (widespread)]	367	Sensory, cognitive, metabolic, immune signaling [63–65].	Some (e.g., β1-AR) [66]	Cardiac failure (e.g., β1-AR knockout) [66]	High
Adrenergic receptors [sympathetic nervous system, heart, vasculature]	9 (α1A/B/D, α2A/B/C, β1, β2, β3)	Regulation of cardiovascular tone, cardiac output, vascular resistance, and metabolic mobilization [66].	Yes (β1-AR) [66]	Severe bradycardia, impaired cardiac contractility, heart failure [66]	Moderate (partial cross-compensation among α/β subtypes)
Serotonin (5-HT) receptors [CNS, GI tract, vasculature]	14	Mood, cognition, GI, vascular tone [67].	Yes (5-HT2C) [83]	Seizure susceptibility, early death [83]	Low
Cannabinoid receptors [CNS, immune system]	2	Neuromodulation, immune regulation [68].	No	Altered immune/neurologic tone [68]	High
Olfactory receptors [odorant detection chemosensation]	Hundreds	Sensory; expressed in non-olfactory tissues [69].	No	Sensory loss only [69]	High
Nuclear receptors (e.g., GRα, MR, PPARs, ER, AR, TR, VDR) [nucleus (widespread)]	48	Ligand-activated transcriptional regulators controlling metabolism, development, and inflammation [70].	Yes (GRα, MR) [58, 83]	GRα: multisystem failure; MR: salt wasting, vascular collapse [58, 84]	GRα: none; MR: low
Receptor tyrosine kinases (RTKs) [cell membranes of endocrine, metabolic, and growth-regulated tissues]	~20 families (e.g., insulin, IGF-1, EGF, VEGF receptors)	Regulate cell growth, metabolism, differentiation, and survival via phosphorylation cascades (e.g., MAPK, PI3K/Akt).	Yes (insulin receptor)	Neonatal hypoglycemia, metabolic failure, impaired growth	Low to moderate
Ligand-gated ion channel receptors (ionotropic) [neuronal membranes]	Various	Fast neurotransmission, neuromuscular signaling [71].	Yes (e.g., NMDA) [92]	Neuronal apoptosis, early lethality [92]	Low to moderate
NMDA receptors [CNS (synapses)]	Multiple	Synaptic plasticity, learning, neurodevelopment [92, 93].	Yes [92]	Neurodegeneration, perinatal lethality [92]	Low

Table 2. Major human receptor families: types and functions. (*continued*)

Receptor family [primary location]	Number of types/Subtypes	Primary function	Survival-critical?	Loss consequences	Redundancy level
Sensory receptors [skin, eyes, ears, viscera]	Multiple	Detection of internal and external stimuli [72].	No	Impaired sensory perception [72]	High
T cell receptors (TCRs) [T lymphocytes]	Millions	Adaptive immunity, antigen recognition [73].	No	Immunodeficiency [73]	High
Toll-like receptors (TLRs) [macrophages, dendritic cells]	~10	Innate immunity, pathogen recognition [74].	No	Impaired innate response [74]	High
TREMs [several]	Several	immune regulation, inflammation control [75].	No	Impaired inflammation regulation [75]	High
Cytokine receptors (e.g., IL-1R, IL-2R, TNFR) [Immune and epithelial cells]	Many	Immune activation, inflammation, cell survival [76].	No	Dysregulated immunity [76]	High
Adenosine receptors (P1 purinergic, GPCR subclass) [CNS, vasculature, immune cells]	Multiple	Pain modulation, immune, vascular tone [77].	No	Reduced nociception, altered perfusion [77]	High
Neuropeptide Y receptors—GPCR subclass	Y1–Y3	Appetite, stress response, circadian rhythms [78].	No	Metabolic dysregulation [78]	High
Presynaptic GPCR (e.g., GABA$_B$, 5-HT1B) [presynaptic terminal in CNS]	Various	Neurotransmitter feedback regulation [79].	No	Altered synaptic signaling [79]	High
Angiotensin receptors, GPCR subclass [kidneys, vasculature, brain]	AT1, AT2	Cardiovascular, renal, CNS function [80].	No	Hypertension, metabolic shifts [80]	Moderate
Common γ-chain (CD132, IL-2RG subunit) [lymphoid tissues]	Shared subunit	Lymphocyte development; shared component of IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 receptor complexes [81].	Yes [81]	Severe combined immunodeficiency [81]	None
KISS1R (kisspeptin receptor, GPCR subclass) [hypothalamus]	Single	Regulate reproductive axis activation and puberty [82].	No	Infertility, delayed puberty [82]	Moderate

This table categorizes major receptor families in the human body by structural classification, number of subtypes, physiological location, primary functions, and relevance to survival and redundancy. Receptors are grouped into membrane-bound (e.g., GPCRs, ionotropic channels), cytoplasmic, and nuclear families, reflecting their distinct yet coordinated roles in cellular signaling and systemic regulation. The "number of types/subtypes" column denotes recognized functional isoforms. The "primary location" and "primary function" columns summarize tissue distribution and physiological role. AR: androgen receptor; CNS: central nervous system; ER: estrogen receptor; GI: gastrointestinal; GRα: glucocorticoid receptor alpha; IGF-1: insulin-like growth factor 1; IL-1R: interleukin-1 receptor; IL-2R: interleukin-2 receptor; IL-2RG: interleukin-2 receptor gamma chain; NMDA: *N*-methyl-*D*-aspartate; KISS1R: kisspeptin receptor; MR: mineralocorticoid receptor; PPARs: peroxisome proliferator-activated receptors; TREMs: triggering receptor expressed on myeloid cells; TR: thyroid hormone receptor; TNFR: tumor necrosis factor receptor; VDR: vitamin D receptor; VEGF: vascular endothelial growth factor.

While these receptors vary widely in structure and mechanism, they are presented together here to illustrate the full spectrum of receptor specialization and functional indispensability, from rapid membrane-bound signaling to genomic regulation via intracellular pathways.

While many function within overlapping networks that provide functional redundancy, others exhibit high specialization with limited or no compensatory mechanisms—making their preservation essential for life. This spectrum—from highly redundant to uniquely indispensable—forms the foundation for understanding the diversity of receptor-mediated control in human biology. Table 2 categorizes major receptor families by structural classification, number of recognized types or subtypes, physiological location, primary functions, and relevance to survival and redundancy. It further distinguishes membrane-bound [e.g., G protein-coupled receptors (GPCRs), ionotropic channels], cytoplasmic, and nuclear families, highlighting their coordinated roles in cellular signaling, tissue distribution, and systemic regulation—underscoring their diversity, specialization, and, for a select few, survival-critical functions.

Immune-specific receptors, such as Toll-like receptors (TLRs), cytokine receptors [e.g., interleukin-1 receptor (IL-1R), IL-6R, TNFR], T cell receptors, and TREMs, initiate inflammation, pathogen sensing, and immune cell activation. These families are central to innate and adaptive immune defense. By contrast, pleiotropic GPCR subclasses—such as adenosine (P1 purinergic) and angiotensin (AT1, AT2) receptors—bridge immune, cardiovascular, and metabolic signaling. Although not exclusive to immune pathways, they influence inflammation, vasomotor tone, and neuroimmune communication. Insulin receptors, part of the receptor tyrosine kinase (RTK) family, primarily regulate metabolic and endocrine signaling and are discussed separately from immune receptors due to their distinct structural and regulatory properties.

G protein-coupled receptors

GPCRs represent the most abundant receptor family in humans, with approximately 367 receptors for endogenous ligands, excluding several hundred olfactory GPCRs. They participate in virtually all physiological processes, including sensory perception, cognitive function, muscle contraction, metabolic regulation, vascular tone, and immune signaling. More than 90% of non-olfactory GPCRs are expressed in the brain, where they display both cell-specific and region-specific expression patterns. Their extensive expression and functional diversity make them primary pharmacological targets in the treatment of cancer, metabolic syndromes, psychiatric disorders, and neurodegenerative diseases [63–65].

Major subgroups include the adrenergic receptor family in humans, which mediates sympathetic nervous system signaling [66], serotonin (5-HT) receptors involved in mood and gut motility [67], and cannabinoid receptors, which modulate neuro-immune balance [68]. While many GPCRs exhibit functional redundancy, some subtypes are non-redundant and essential for survival. For example, loss or dysfunction of the β1-adrenergic receptor (β1-AR) impairs cardiac contractility and reduces cardiac output, contributing to the development of heart failure [88, 89]. Intriguingly, certain olfactory GPCRs, traditionally associated with smell, also perform functional roles in peripheral organs, such as the kidney and heart, suggesting broader physiological relevance beyond the nasal epithelium [69].

Nuclear and ion channel receptors

Nuclear receptors, 48 of which have been identified in humans, function as ligand-activated transcription factors that regulate metabolism, development, and immune homeostasis [70]. Their ability to directly influence gene expression makes them central to long-term physiological adaptations and key targets in endocrine, metabolic, and inflammatory disorders.

Ion channel receptors, including nicotinic acetylcholine receptors, mediate rapid synaptic transmission, playing critical roles in neuromuscular coordination, sensory processing, and autonomic regulation [71]. These receptors are major therapeutic targets in neurodegenerative diseases, epilepsy, pain syndromes, and addiction disorders [71].

Sensory and immune receptors

Sensory receptors convert environmental stimuli into neural signals across exteroceptive, interoceptive, and proprioceptive modalities, enabling precise detection of external and internal changes [72]. Their integration with central neural circuits allows rapid behavioral and physiological responses to environmental challenges.

The immune system employs specialized receptor families to maintain immune surveillance and coordinate host defense. These include T cell receptors (TCRs), which mediate antigen-specific adaptive immunity; TLRs, which detect pathogen-associated molecular patterns and initiate innate immune responses; and triggering receptors expressed on myeloid cells (TREMs), which fine-tune inflammatory activity and tissue repair, and resolution [73–75].

Other receptor families

Additional receptor families hold critical roles in maintaining systemic balance. Cytokine receptors—such as the IL-1R—mediate key immune signaling pathways and orchestrate inflammatory responses [76]. Adenosine and neuropeptide Y receptors modulate metabolic homeostasis and neurological functions [78]. Insulin receptors regulate glucose uptake and anabolic metabolism, whereas angiotensin receptors control vascular tone and fluid balance, maintaining cardiovascular stability [80].

Essential vs. redundant receptor systems

Although receptor systems underpin nearly all physiological processes, genetic knockout and functional disruption studies reveal that only a small subset is truly non-redundant for postnatal survival. Most operate within overlapping networks, allowing partial compensation when one pathway is impaired. In contrast, survival-critical receptors—such as GRα—cannot be substituted; their loss precipitates rapid systemic collapse, multi-organ dysfunction, and postnatal death [90]. This distinction underscores the evolutionary and clinical significance of these non-redundant receptors, whose preservation is essential for organismal viability.

Although GRα signaling is essential for survival, its effects are context-dependent. Excessive or prolonged activation can trigger apoptosis in specific cell types, particularly thymocytes and lymphocytes, whereas GRα deficiency leads to systemic failure. Physiological homeostasis, therefore, depends on preserving a balanced range of GRα activity [90, 91].

The distinction between redundant and non-redundant receptor systems offers a crucial framework for understanding physiological resilience. While most receptors operate within overlapping networks capable of compensating for partial loss, a select few are uniquely essential—without them, survival beyond birth becomes impossible. These non-redundant receptors support systemic stability; each handles vital processes that no other pathway can fully replace. The next section highlights essential non-steroid receptors, detailing their organ-specific roles and the systemic consequences that result from their absence.

Essential non-steroid receptors for postnatal survival

Among hundreds of receptor systems in the human body, only a small subset of non-steroidal receptors is truly indispensable for life after birth. Genetic knockout and targeted pharmacological studies consistently identify several standouts—most notably *N*-methyl-*D*-aspartate (NMDA) receptors, receptor-interacting protein kinase 1 (RIPK1), and 5-HT$_2$C serotonin receptors—whose complete loss precipitates rapid systemic collapse and early mortality. Each of these receptors performs irreplaceable functions in maintaining neural excitatory balance, orchestrating immune regulation, and safeguarding metabolic stability. Their non-redundant status places them among the most vital components of the receptor network, underscoring the principle that survival depends not on the sheer number of receptors, but on the unique integrative functions of a select few.

NMDA receptors and neuronal viability

NMDA receptors are among the most clearly defined essential receptors for postnatal survival, playing a non-substitutable role in neuronal viability and the formation of functional neural circuits. Their activation governs synaptic plasticity, neuronal differentiation, migration, and the balance between excitatory and inhibitory connectivity within developing networks. Genetic deletion of the obligatory NMDAR1 subunit in mice produces widespread thalamic apoptosis and postnatal lethality [92]. Similarly, pharmacologic blockade of NMDA receptors during late fetal or early neonatal development—using agents such as MK-801 or phencyclidine—induces extensive apoptotic neurodegeneration, particularly in cortical and limbic regions [93].

Synaptic NMDA receptor activation supports neuronal viability by initiating transcriptional programs that upregulate pro-survival genes and suppress apoptotic signaling pathways. This neuroprotective effect is attributed mainly to receptor localization at synaptic sites. In contrast, activation of extrasynaptic NMDA receptors triggers neurotoxic cascades linked to excitotoxicity (neuronal injury resulting from excessive glutamate receptor stimulation and sustained calcium influx), which activate intrinsic cell-death pathways [94–96].

Disruption of NMDA receptor signaling impairs neuronal differentiation, delays cellular maturation, and hinders the integration of new neurons into established circuits. These deficits are particularly pronounced during the maturation of interneurons and the refinement of inhibitory synapses [97–99]. NMDA receptors mediate both ionotropic (ion-flux-dependent) and metabotropic (ion-independent) signaling, each regulating transcriptional, structural, and metabolic programs essential for neuronal development and connectivity [100, 101]. The dynamic balance between synaptic and extrasynaptic receptor activity, therefore, acts as a molecular switch determining whether neurons survive or undergo degeneration [94, 95].

Beyond their role in synaptic function, NMDA receptors play a crucial part in early brain development, particularly during neuronal migration and cortical layering, which occurs before synaptogenesis. Their activity determines the spatial positioning and temporal sequencing of neuronal integration during cortical development, also known as corticogenesis [102, 103]. Collectively, these findings establish NMDA receptors as indispensable for postnatal viability by sustaining neuronal survival, guiding developmental integration, and maintaining excitatory-inhibitory balance.

RIPK1 and immune-epithelial integrity

RIPK1 is a cytoplasmic signaling protein that determines cell fate through a dual functional modality. Its kinase activity promotes inflammation and programmed cell death, whereas its scaffold function—serving as a structural platform to assemble and stabilize signaling complexes without initiating cell death—preserves tissue integrity by preventing inappropriate apoptosis and necroptosis [104, 105].

RIPK1 knockout mice exhibit early postnatal lethality from uncontrolled systemic inflammation, even in the absence of other death-pathway mediators, underscoring its essential, non-redundant role in immune and tissue homeostasis [106, 107]. Its regulatory balance is maintained by upstream kinases such as adenosine monophosphate-activated protein kinase (AMPK) and Unc-51-like kinase 1 (ULK1), which suppress its pro-death signaling under metabolic stress [108, 109].

RIPK1 also interfaces with central inflammatory signaling hubs—including NF-κB, TANK-binding kinase 1 (TBK1), and the inflammasome complex—that integrate upstream danger signals and coordinate downstream inflammatory responses. Dysregulation of RIPK1 within these pathways can disrupt epithelial barrier function and precipitate rapid, often fatal, systemic inflammation [110, 111]. Collectively, these findings establish RIPK1 as a survival-critical signaling node whose precise regulation is indispensable for immune balance and epithelial integrity in postnatal life.

5-HT$_2$C serotonin receptor and seizure susceptibility

The serotonin 5-HT$_2$C receptor (HTR2C) is a non-redundant, survival-critical receptor whose loss leads to severe neurological consequences. Genetic deletion of HTR2C in mice causes progressive, adult-onset epilepsy and premature death from seizure activity, with a pronounced male predominance [112]. Although HTR2C is highly expressed in GABAergic neurons, targeted deletion within these cells does not prevent seizure onset, indicating that its protective role extends beyond GABAergic circuits and reflects broader network-level homeostatic mechanisms.

In humans, HTR2C genetic variants are overrepresented in cases of sudden unexpected death in epilepsy (SUDEP), and may also contribute to susceptibility in male-predominant sudden infant death syndrome (SIDS), suggesting a sex-dependent neuroprotective function that is critical for postnatal neural stability [113]. The indispensable role of HTR2C in suppressing seizures and supporting neurodevelopment reinforces its classification as a survival-essential receptor required for maintaining postnatal neural integrity.

Synthesis and implications

These findings emphasize that a small, specific group of non-steroidal receptors—including NMDA receptors, RIPK1, and the 5-HT$_2$C serotonin receptor—are indispensable for postnatal survival. Their essentiality arises not from narrow, isolated functions but from their integrated roles in preserving neuronal viability, maintaining immune-epithelial integrity, and sustaining systemic physiological stability across multiple organ systems. Disruption of these receptors—whether through genetic deletion or pharmacologic inhibition—results in severe consequences, including widespread neurodegeneration, immune and epithelial system failure, or network-level seizure susceptibility, often progressing to rapid postnatal death despite otherwise intact physiology.

The rare class of non-redundant receptors outlined above—whose loss precipitates catastrophic postnatal failure—illustrates that survival after birth depends on a small number of molecular systems positioned at the apex of physiological regulation. Within this context, the GRα emerges as an equally indispensable integrator, distinguished by a far broader sphere of influence. Unlike NMDA receptors, RIPK1, or 5-HT$_2$C, whose criticality is anchored mainly to specific domains, such as neuronal viability, immune-epithelial stability, or seizure prevention, GRα coordinates an extensive, interlinked network encompassing stress responses, immune regulation, hemostasis, metabolic adaptation, mitochondrial function, circadian rhythms, neural signaling, and tissue repair. Acting through the glucocorticoid—GRα system, it fine-tunes homeostatic corrections across all organ systems and circulating cell populations, ensuring not only immediate survival under acute stress but also long-term physiological stability [6].

GRα as a non-redundant integrator of systemic homeostasis

GRα blockade reveals multisystem fragility

The non-redundant, integrative role of GRα in maintaining systemic homeostasis is most clearly demonstrated by experimental models and clinical studies involving its pharmacological inhibition. One such approach involves direct GR blockade using mifepristone(RU-486), a well-characterized antagonist that competitively inhibits cortisol binding and suppresses receptor-mediated transcription. Structural studies show that mifepristone induces an antagonist conformation in GRα, favoring corepressor recruitment over coactivator engagement, thus silencing glucocorticoid-responsive gene expression. This mechanism explains its therapeutic value in conditions of glucocorticoid excess, such as Cushing's syndrome, while simultaneously exposing the system-wide vulnerabilities that arise when GRα is inhibited.

In the central nervous system (CNS), GR antagonism can reverse stress-induced suppression of neurogenesis, yet prolonged exposure increases the risk of neuronal injury and photoreceptor degeneration in preclinical models [114–116]. Outside the brain, GR blockade impairs lipid metabolism by downregulating intestinal lipase expression, underscoring GR's essential role in digestive and metabolic homeostasis [117]. Systemically, mifepristone-induced GR inhibition leads to hyperactivation of the HPA axis, with elevated adrenocorticotropic hormone (ACTH) and cortisol, and increases the risk of adrenal insufficiency [118–120].

These multisystem disruptions—spanning cardiovascular, immune, metabolic, neuroendocrine, respiratory, renal, hepatic, musculoskeletal, gastrointestinal, vascular, and neural domains—underscore GRα's role as an irreplaceable integrator of homeostasis. Pharmacologic inhibition of GRα exposes the fragility of interdependent physiological systems, demonstrating that preserving GRα function is critical to avert systemic collapse, sustain postnatal survival, and maintain long-term physiological stability.

DNA-binding-independent functions support viability

While pharmacological blockade highlights GRα's role in transcriptional control, genetic loss-of-function models provide deeper insights into its structural flexibility and functional versatility. These models confirm that GRα is indispensable for both stress adaptation and the maintenance of stability across multiple organ systems. Clinical and experimental studies further link GR disruption to behavioral changes, fluid and electrolyte imbalance, and impaired inflammatory resolution, reinforcing its status as a non-redundant survival regulator [121].

Notably, the survival in GR^{dim} mice—engineered to lack DNA-binding and dimerization capacity—demonstrates that viability can be sustained through GRα mechanisms independent of GRE-mediated transcription. These mice remain viable because key non-genomic signaling and transrepression pathways are preserved. In particular, GR^{dim} retains the ability to repress pro-inflammatory transcription factors such as AP-1 and NF-κB through direct protein-protein interactions, even in the absence of GRE binding. Such non-classical mechanisms are sufficient to avert the lethal phenotype seen in complete GR knockouts, underscoring GRα's foundational role in both individual organ-specific regulation and the coordination of inter-organ signaling required for systemic homeostasis [122].

Conditional knockout models reveal GRα as a multi-system survival axis

Tissue-specific GR knockout models underscore GRα's critical and non-redundant role in sustaining stability both within and between organ systems.

Cardiomyocyte-specific deletion produces severe myocardial hypertrophy, impaired ventricular function, and early mortality from progressive heart failure, demonstrating GRα's essential contribution to cardiovascular resilience under stress [123]. Beyond organ-specific failure, systemic GRα loss triggers persistent inflammation from impaired immune regulation, mitochondrial dysfunction with reduced ATP generation, and collapse of neuroendocrine mechanisms that maintain vascular tone—culminating in hemodynamic instability and multi-organ failure [61, 124].

Hepatic-specific deletion produces marked defects in gluconeogenesis, lipid handling, and insulin sensitivity—effects that are more severe than those observed in adipose-specific deletion—indicating that hepatic GRα serves as a primary metabolic control node [125].

In skeletal muscle, GRα deletion prevents glucocorticoid-induced atrophy by blocking MuRF1 and atrogin-1 activation but disrupts systemic energy balance by impairing protein turnover and shifting metabolic load to the liver and adipose tissue [126].

Antagonistic MR interplay and tissue-specific modulation

In contrast to the severe phenotypes described in Conditional knockout models reveal GRα as a multi-system survival axis, cardiomyocyte-specific deletion of the MR does not result in cardiac dysfunction. Mice lacking MR in the heart maintain normal cardiac structure and function even under physiological stress [123], indicating that MR is not essential for baseline cardiovascular viability. However, combined GRα-MR deletion produces less severe cardiac impairment and systemic deterioration than GRα deletion alone, suggesting that unopposed MR signaling can be maladaptive in the absence of GRα, and that MR removal can partially buffer these effects [123].

Mechanistic evidence reinforces this antagonistic interplay: MR activation reduces GRα responsiveness by upregulating FK506-binding protein 5 (FKBP5), a molecular chaperone that restricts GRα's transcriptional activity and dampens cardiovascular reactivity [85]. MR and GRα also act cooperatively across other tissues, including skin and brain, to regulate inflammatory responses. Rather than functioning interchangeably, they exert distinct yet complementary roles, with combined deletion leading to exacerbated inflammation and structural abnormalities [127, 128].

Mechanistically, MR and GRα can co-occupy chromatin and influence transcriptional programs; however, MR more often modulates or attenuates GRα-driven gene expression, primarily through FKBP5 upregulation [83, 85]. Their interaction is best described as modulatory or antagonistic rather than synergistic. While both receptors contribute to stress adaptation, MR cannot substitute for GRα's systemic integrative functions. This distinction is further underscored in mammary epithelial cells, where GRα signaling supports cell survival, and its withdrawal leads to apoptosis, demonstrating GRα's context-specific control over cellular viability [129].

Glial models extend this understanding to the peripheral nervous system. Although direct GRα deletion in Schwann cells has not yet been reported, MR knockout in these cells induces compensatory GRα upregulation, alters the myelin sheath structure and nerve conduction, and highlights GRα's likely role in maintaining neuroimmune balance and myelination. These findings reinforce GRα's capacity to preserve peripheral nerve integrity when other steroid receptors fail, underscoring its role as a neural survival safeguard [23].

Functional crosstalk with PPARα and its boundaries

Although GRα is largely a non-redundant systemic integrator, limited functional convergence can occur through crosstalk with other NRs, most notably PPARα, extensively studied in hepatic and cardiac tissues. GRα and PPARα can form heterodimeric complexes—two distinct NRs binding cooperatively to DNA—or co-regulate target genes via shared enhancer response elements, thereby preserving select functions related to metabolic regulation and inflammation resolution [130, 131]. Activation of PPARα has been shown to attenuate glucocorticoid-induced metabolic side effects and enhance the transcriptional repression of pro-inflammatory genes, reinforcing the concept of context-dependent convergence between NRs [130].

Additional interactions between GRα and other NRs, such as retinoic acid receptors (RARs) and estrogen receptor alpha (ERα), have also been reported, potentially modulating GRα-regulated networks through enhancer competition or cooperative occupancy of chromatin regulatory elements [132]. However, these interactions remain highly tissue-restricted and cannot reproduce the systemic integrative capacity that uniquely defines GRα.

Agonism of PPARα provides both anti-inflammatory and metabolic benefits; however, current evidence does not support its ability to rescue survival or prevent organ failure in GRα-deficient or glucocorticoid-resistant states. Most protective effects from PPARα activation—such as enhanced cardiac function in sepsis or suppression of NF-κB-driven cytokines—require intact GRα signaling for full efficacy [85, 133–135]. In models of erythropoietic stress and systemic inflammation, PPARα and GRα cooperate synergistically to reinforce transcriptional repression and promote hematopoietic progenitor self-renewal [130]. This synergy deteriorates when GRα is absent or dysfunctional, and no experimental evidence indicates that PPARα agonists alone can restore systemic homeostasis in the absence of GRα. Moreover, in glucocorticoid-resistant states where GRα signaling is diminished, PPARγ—not PPARα—is preferentially upregulated, further diminishing the plausibility of PPARα as a compensatory survival pathway [136, 137]. Thus, while PPARα can assist GRα in maintaining metabolic and immune stability, it cannot substitute for GRα's non-redundant roles in stress adaptation, developmental programming, and organismal survival.

In the liver, PPARα activation stimulates fatty acid oxidation and ketogenesis during fasting or metabolic stress, partially mirroring GRα's metabolic functions [130, 138]. In polymicrobial sepsis models, PPARα activation improves cardiac energy metabolism and enhances survival, demonstrating its ability to promote local tissue resilience [137]. However, despite these functional intersections, PPARα cannot compensate for GRα's broader regulatory roles in immune modulation, neuroendocrine coordination, or developmental programming [134, 135]. Overall, PPARα-mediated compensation is limited, highly context-dependent, and insufficient to prevent the systemic collapse observed in GRα-deficient states.

Cooperative transcriptional regulation by GRα and PPARα in hepatic and immune cells depends on the recruitment of specific chromatin-associated co-regulators—proteins that modify chromatin architecture or interface with the transcriptional machinery to facilitate or repress gene expression. Among these, phosphorylated AMP-activated protein kinase (phospho-AMPK) plays a pivotal role. During prolonged fasting, phospho-AMPK is selectively directed to promoters co-occupied by GRα and PPARα, enabling the coordinated activation of key metabolic genes. Pharmacologic inhibition of AMPK impairs this transcriptional synergy, underscoring its role as a molecular switch that governs NR crosstalk [138].

In parallel, chromatin remodelers—enzymatic complexes that restructure DNA-protein interactions to increase transcription factor accessibility—play key roles in supporting NR activity. Among these, the

SWI/SNF complex, which uses ATP hydrolysis to remodel nucleosomes and enhance transcriptional accessibility, is particularly relevant. Its BAF60b/SMARCD2 subunit has been shown to promote PPARα-driven transcriptional programs in hepatic metabolism and immune cell differentiation [139–141]. Other chromatin remodelers, such as INO80, which facilitates transcriptional regulation and DNA repair under stress, and the NuRD complex—a repressive assembly that silences gene activity by removing histone acetylation marks—may also contribute to NR signaling. However, direct evidence linking INO80 or NuRD to GRα-PPARα co-regulation remains limited [142].

These mechanistic insights underscore the conditional and limited scope of PPARα-mediated compensation. Without the coordinated recruitment of chromatin remodelers and metabolic co-regulators such as AMPK, the functional synergy between GRα and PPARα cannot be established. Consequently, while PPARα may enhance GRα activity in specific metabolic or inflammatory contexts, it cannot substitute for GRα in states of receptor deficiency or glucocorticoid resistance. Clinically, PPARα agonists such as fenofibrate and bezafibrate are approved for dyslipidemia, but they have not demonstrated therapeutic efficacy in systemic inflammatory or stress-related disorders. Although PPARα activation may support mitochondrial energy production [143] and modestly reduce inflammation during critical illness [144], it remains an incomplete and insufficient compensatory pathway.

Essential functions and integrated roles of the MR in stress, immunity, and homeostasis

To establish a coherent foundation for understanding receptor-specific mechanisms, this section outlines the complementary and opposing roles of GRα and MR in maintaining systemic and tissue-specific homeostasis. These two receptors operate in parallel but distinct regulatory domains—GRα orchestrates systemic integration across immune, metabolic, and vascular systems, whereas MR governs localized electrolyte and inflammatory balance at the tissue level. Their coordinated activity maintains whole-body homeostasis under physiological conditions, while their imbalance underlies the dual pathology of systemic collapse from GRα loss and localized dysfunction driven by MR overactivation.

It is important to note that, while MR overactivation drives inflammatory and fibrotic injury in critical illness, complete MR deficiency—observed only in experimental or congenital models—also results in postnatal lethality due to profound electrolyte imbalance and circulatory failure. Thus, pathological outcomes depend on whether MR signaling is excessive or absent, whereas GRα loss uniformly results in systemic collapse.

In contrast, within the CNS, the polarity of receptor regulation is reversed. Under baseline conditions, MR activity predominates, sustaining neuronal excitability, stress resilience, and emotional stability, whereas GRα is transiently activated during acute stress. Sustained GRα hyperactivation or MR deficiency in the CNS produces maladaptive neural responses, oxidative stress, and neuronal injury—a tissue-specific disruption distinct from the systemic pattern of GRα loss and MR overactivation. Accordingly, both GRα and MR overactivation can lead to pathology, but through distinct mechanisms: MR overactivation drives vascular inflammation and fibrotic injury in peripheral tissues, whereas GRα overactivation in the CNS induces neuroinflammatory and excitotoxic responses.

This interplay between systemic GRα signaling and localized MR activity, and their respective contributions to homeostatic balance and disease, is illustrated in Table 3 [16, 58, 83–87, 145, 146]. Complete loss or severe impairment of GRα or MR signaling leads to early postnatal death due to failure of essential stress-adaptive, metabolic, and electrolyte-regulatory mechanisms. This lethality underscores the indispensable role of both receptors in sustaining systemic stability after birth, even though their pathological manifestations diverge in disease states—GRα loss resulting in systemic collapse and MR overactivation producing localized inflammation and fibrosis.

Immune collapse: the role of MR in immune competence

Although traditionally studied in the context of electrolyte homeostasis and renal physiology, the MR is now recognized as a pivotal regulator of immune function. MR is expressed across multiple immune lineages—

Table 3. Comparative roles of GRα and MR across physiological systems and disease states.

Physiological system	GRα—key functions	MR—key functions	Pathogenic imbalance/Clinical consequence
Systemic integration	Master regulator of whole-body homeostasis; coordinates stress adaptation, metabolism, and mitochondrial energy production [58, 83, 84].	Maintains electrolyte and volume balance; sustains baseline vascular tone [16, 86].	↓ GRα → systemic inflammation, mitochondrial failure, and cardiovascular collapse [83]; ↑ MR → hypertension, vascular inflammation, fibrosis [16].
Immune system	Represses excessive inflammation, promotes resolution, restores immune tolerance [83, 85].	Supports macrophage survival and innate immune activation [85, 87].	↓ GRα + ↑ MR → persistent inflammation, cytokine excess, impaired resolution [83, 85].
Cardiovascular/renal	Preserves endothelial integrity via eNOS activation and anti-inflammatory signaling [83, 86].	Regulates sodium retention, blood pressure, and vascular reactivity [16, 86].	↓ GRα → endothelial dysfunction and vascular leakage [83]; ↑ MR → fibrosis, oxidative stress, and cardiometabolic injury [16].
Metabolic/hepatic	Enhances gluconeogenesis under stress; maintains glucose and lipid balance [83, 84].	Modulates insulin sensitivity and adipose inflammation [16].	↓ GRα → energy failure and hypometabolism [83]; ↑ MR → adipose inflammation and insulin resistance [16].
CNS/neuroendocrine	Facilitates stress adaptation, neuroplasticity, and emotional regulation [145, 146].	Maintains basal excitability, circadian tone, and neuroendocrine stability [146].	↑ GRα or ↓ MR → neuroinflammation, oxidative stress, excitotoxicity [145, 146].
Developmental/survival	Required for postnatal viability; integrates transcriptional and non-genomic responses essential for stress tolerance [83, 145].	Supports perinatal electrolyte and circulatory adaptation [86].	Deletion of either → postnatal death (GRα = systemic failure; MR = salt-wasting collapse) [83, 86].

This table compares the complementary and opposing actions of GRα and MR across major physiological systems. GRα functions as the master integrator of whole-body homeostasis, coordinating metabolic, vascular, immune, and neuroendocrine responses required for stress adaptation and survival. MR primarily maintains electrolyte balance, vascular tone, and tissue-specific homeostasis. Loss of GRα results in multisystem failure, characterized by metabolic and immune collapse, whereas MR loss causes localized salt-wasting and vascular inflammation. Their imbalance underlies many critical-illness phenotypes, where GRα deficiency leads to systemic collapse and MR overactivation promotes inflammation and fibrosis. GRα: glucocorticoid receptor alpha; MR: mineralocorticoid receptor; eNOS: endothelial nitric oxide synthase; CNS: central nervous system. ↑: increased; ↓: decreased; →: leads to/results in.

including macrophages, monocytes, T cells, and B cells—where it modulates cellular phenotype, activation thresholds, and cytokine production. In macrophages, MR activation promotes polarization toward the pro-inflammatory M1 phenotype, enhancing pathogen clearance and reinforcing the innate immune response under stress. In T lymphocytes, MR signaling promotes differentiation into Th1 and Th17 effector subsets while inhibiting the development and function of regulatory T cells (Tregs). This dual effect amplifies systemic inflammation and reduces immune tolerance, particularly in chronic inflammation or autoimmunity.

Loss or pharmacologic inhibition of MR profoundly disrupts these immune dynamics. MR deletion impairs macrophage survival and their ability to establish and maintain tissue residency—the process by which immune cells localize within specific organs and persist in a functional state—leading to increased apoptosis and defective myeloid lineage differentiation [147]. These alterations weaken innate immune defenses, delay recovery from infection or injury, and impair emergency myelopoiesis during systemic inflammation.

Furthermore, MR blockade decreases monocyte recruitment and reshapes the cytokine signaling landscape—typically suppressing pro-inflammatory mediators such as IL-6 and TNF-α while enhancing anti-inflammatory cytokines like IL-10. This shift drives macrophages and T cells toward anti-inflammatory phenotypes—thereby limiting tissue injury in experimental models of cardiovascular, renal, and autoimmune disease [8, 16, 147].

In disease contexts, MR overactivation acts as a potent driver of chronic inflammation and progressive immune-mediated tissue injury. In cardiovascular tissues, excessive MR signaling amplifies inflammatory cascades, promotes collagen deposition, and accelerates fibrotic remodeling, thereby contributing to the pathogenesis of atherosclerosis, vascular stiffness, and heart failure [148, 149]. Similarly, in renal tissues, MR activation induces macrophage-driven inflammation and fibrosis, exacerbating chronic kidney disease. Conversely, MR antagonism mitigates these pathological effects, preserving tissue architecture and organ function [16, 150]. Pharmacologic inhibition of MR not only reduces immune cell infiltration and suppresses pro-inflammatory cytokine production in both vascular and renal tissues, but also highlights its therapeutic potential in chronic inflammatory conditions [16, 147].

Together, these findings position MR as a critical immunomodulatory receptor, essential for maintaining immune homeostasis and directly implicated in the progression of chronic inflammatory disease. MR's indispensable roles in macrophage survival, T cell polarization, and cytokine regulation establish it as a central integrator of hormonal and immune signaling. These functions underscore MR's translational relevance as a therapeutic target in autoimmune, cardiovascular, and renal diseases, where selective antagonism may restore immune balance without disrupting systemic homeostasis.

Disruption of cardiometabolic homeostasis

The MR plays a pivotal role in maintaining cardiovascular and metabolic homeostasis. Beyond its classical role in renal sodium reabsorption, MR influences vascular tone, cardiac remodeling, insulin sensitivity, and adipose tissue metabolism. Pathological MR overactivation—arising from hormonal excess, metabolic stress, or aging—drives inflammation, oxidative stress, and extracellular matrix (ECM) remodeling, thereby linking endocrine dysregulation to the pathogenesis of cardiometabolic disease.

MR is expressed in vascular smooth muscle cells, endothelial cells, and cardiomyocytes. In the vasculature, excessive MR activation impairs endothelial function by reducing nitric oxide bioavailability, increasing vasoconstriction, and promoting arterial stiffness. Under conditions of metabolic stress or aging, these effects culminate in progressive endothelial dysfunction and adverse vascular remodeling, accelerating the development of hypertension, heart failure, and atherosclerosis [150–152].

In the myocardium, MR signaling induces pro-inflammatory cytokine production, collagen deposition, and cardiomyocyte hypertrophy—processes that drive the progression of heart failure, myocardial infarction, arrhythmias, and structural heart disease [151, 153, 154]. In parallel, MR overactivation amplifies oxidative damage and ECM accumulation, promoting valvular dysfunction and atherosclerotic plaque formation [155, 156].

These integrated vascular and myocardial effects position MR as both a hormonal effector and a pathogenic amplifier in cardiometabolic disease. Accordingly, MR antagonists have demonstrated clear clinical benefits in heart failure with preserved ejection fraction, resistant hypertension, and diabetic cardiomyopathy [157].

MR is also expressed in adipose tissue, where it regulates adipocyte differentiation, lipid storage, and glucose metabolism. Pathological MR overactivation promotes visceral fat accumulation, insulin resistance, and secretion of a pro-inflammatory adipokine profile, creating a feed-forward loop that amplifies metabolic syndrome [158–160]. This chronic inflammatory milieu fosters the development of obesity, glucose intolerance, and dyslipidemia, further destabilizing metabolic homeostasis.

Pharmacological MR antagonists such as eplerenone and spironolactone attenuate vascular and cardiac fibrosis, improve insulin sensitivity, and lower blood pressure. These agents are clinically effective in the treatment of hypertension, heart failure, obesity, and type 2 diabetes. However, their broader application is limited by the risk of hyperkalemia, particularly in elderly patients or those with renal impairment [153, 160].

In conclusion, MR overactivation disrupts cardiometabolic homeostasis by promoting inflammation, fibrosis, and metabolic dysfunction across vascular, cardiac, and adipose tissues. While MR antagonists provide clinically significant therapeutic benefit, their use requires careful risk-benefit assessment, especially in vulnerable populations.

GR-MR interdependence: a unified axis of stress regulation and survival

The GR and MR form a conserved hormonal signaling axis that is essential for stress adaptation, metabolic stability, and immune regulation across vertebrate species [161, 162]. While GRα is widely recognized for its pleiotropic immunoregulatory and homeostatic functions, MR is increasingly recognized for its expanded roles beyond classical electrolyte balance.

Under physiological conditions, GRα orchestrates both innate and adaptive immunity by regulating immune cell development, trafficking, apoptosis, and cytokine production. This coordinated regulation ensures effective immune surveillance while preventing excessive inflammation through context-dependent transcriptional control. In parallel, MR—initially characterized for its role in electrolyte and fluid homeostasis—has emerged as a key modulator of immune activation pathways. It promotes macrophage polarization toward a pro-inflammatory M1 phenotype, enhances Th1 and Th17 differentiation, and modulates monocyte survival and activation thresholds.

Rather than acting independently, GRα and MR function as a coordinated endocrine-immune axis integrating hormonal signals with immunological responses. Through their interplay, they sustain immune vigilance during stress while preventing maladaptive overactivation that leads to autoimmunity, tissue injury, and loss of homeostatic control. This dual-regulator system represents an evolutionarily conserved survival mechanism in which GRα and MR act as molecular gatekeepers, finely balancing immune activation and resolution to preserve systemic integrity under environmental or physiological stressors.

The preservation of cellular and systemic homeostasis depends critically on the functional integrity of corticosteroid receptors, particularly GRα and MR. As ligand-activated nuclear transcription factors, both govern essential genomic programs in response to glucocorticoids and mineralocorticoids, orchestrating survival-critical processes that maintain metabolic balance, immune regulation, and cardiovascular stability. Evidence from animal models and molecular studies consistently demonstrates that the complete loss or severe impairment of GRα or MR signaling results in early postnatal death from collapse of physiological homeostasis. This systemic failure initiates a cascade of secondary disruptions involving neuronal integrity, immune competence, hemodynamic regulation, and metabolic control [7].

Beyond their overlapping roles in immune and metabolic regulation, GRα and MR also coordinate behavioral and neuroendocrine responses to stress. MR, with its high affinity for glucocorticoids, is predominantly engaged under basal conditions, supporting memory retrieval, threat evaluation, and initial coping responses. In contrast, GRα is activated during peak stress to facilitate recovery, mobilize energy, and consolidate memory. This dynamic MR-GR “switch” forms the basis for adaptive stress regulation and is essential for preserving physiological resilience [163, 164].

Antagonistic and sequential regulation in the brain

Extensive evidence demonstrates that GRα promotes pro-apoptotic signaling under stress while MR supports anti-apoptotic and neurogenic pathways under basal glucocorticoid levels, highlighting their opposing influences on neuronal survival [165–168].

A finely tuned balance between GRα and MR signaling is essential for preserving hippocampal architecture, synaptic plasticity, and overall stress adaptability. Disruption or deficiency of either receptor disturbs this homeostatic equilibrium, heightening vulnerability to excitotoxic injury and accelerating neurodegeneration [169]. At the molecular level, both receptors act through integrated genomic and non-genomic mechanisms that enable rapid and sustained modulation of neuronal function.

Significantly, MR signaling enhances expression of FKBP5, a co-chaperone that locally restrains GRα hyperactivation within the hippocampus. This buffering mechanism preserves synaptic integrity and limits stress-induced neuronal injury [85]. Disruption of this MR-GRα regulatory axis—whether from chronic stress exposure or genetic polymorphisms—compromises stress resilience and increases susceptibility to affective and neuropsychiatric disorders [170, 171].

These receptors also operate in a coordinated temporal sequence during stress. MR is activated first, guiding threat appraisal and the immediate behavioral response, while GRα becomes dominant later, supporting physiological recovery and the consolidation of emotional memory. Disruption of this sequential coordination—through chronic GRα dominance or insufficient MR signaling—impairs emotional regulation and weakens cognitive resilience [163, 170].

From an evolutionary perspective, GRα-mediated neuronal apoptosis may represent an adaptive mechanism that removes irreversibly damaged or energetically inefficient neurons under extreme stress. This selective pruning supports neural circuit remodeling, conserves systemic energy balance, and prevents excitotoxic overload. Emerging evidence indicates that neurons can exhibit transient, reversible apoptotic signaling ("apoptotic pulses"), allowing cell survival and functional recovery if the stressor is resolved promptly. Such dynamic interplay between apoptosis, microglial remodeling, and transcriptional adaptation balances acute cellular sacrifice with long-term resilience in stress-sensitive brain regions [172, 173].

Aging and genetic modulation of GRα-MR signaling

A growing body of evidence demonstrates that GRα and MR function as an integrated regulatory system across the brain and peripheral tissues, shaping stress responsiveness, neuronal survival, and long-term homeostatic stability [83, 84, 145, 146]. MR also contributes to neuronal protection by modulating GRα sensitivity via FKBP5 regulation, a mechanism that limits stress-induced transcriptional overload and helps preserve neuronal plasticity throughout aging [85]. Together, these findings support a model in which GRα and MR operate as a coordinated regulatory axis, with stress resilience and neuroendocrine homeostasis depending on their balanced interplay rather than the dominance of either receptor.

Age-related shifts in GRα and MR expression profoundly influence neuronal sensitivity and plasticity, particularly within neural precursor cell populations. These molecular changes reshape stress responsiveness, adult neurogenesis, and synaptic remodeling throughout the lifespan. Polymorphisms in the GRα and MR genes (*NR3C1* and *NR3C2*, respectively) further modulate this regulatory axis, with certain variants reducing receptor sensitivity or altering expression patterns in the hippocampus and prefrontal cortex. Such genetic differences are associated with dysregulated HPA axis activity and increased vulnerability to depression, post-traumatic stress disorder (PTSD), and cognitive decline, particularly in individuals exposed to early-life adversity or exhibiting sex-specific susceptibility [174–176].

Variants that disrupt GRα or MR signaling contribute to maladaptive neuroendocrine responses and reduced nervous system plasticity [168, 171]. Together, these findings underscore that both developmental timing and genetic background shape corticosteroid signaling, confirming the central role of GRα and MR as lifelong modulators of neurobiological adaptation and stress resilience.

Corticosteroid receptors in the nervous system and systemic vulnerability

Systemic homeostasis and postnatal survival: the essential role of GRα and MR

Complete loss or severe impairment of GRα or MR signaling results in early postnatal death due to the failure of essential stress-adaptive, metabolic, and electrolyte-regulatory mechanisms. This developmental lethality underscores the indispensable role of both receptors in sustaining systemic stability after birth, even though their patterns of dysregulation (GRα loss versus MR overactivation) diverge in disease states. Systemic receptor failure initiates a cascade of disruptions affecting neuronal integrity, immune competence, vascular regulation, and metabolic control. GRα-deficient mice exhibit profound perinatal lethality, primarily due to impaired lung maturation and dysregulation of the HPA axis [90, 177]. These animals also display adrenal cortical hypoplasia, reduced steroidogenic enzyme expression, and impaired hepatic gluconeogenesis—culminating in adrenal insufficiency and life-threatening hypoglycemia [90, 178]. The convergence of respiratory immaturity, hormonal imbalance, and metabolic instability leads to death within hours of birth [90].

MR-deficient mice exhibit severe postnatal electrolyte dysregulation, characterized by life-threatening sodium and water loss that culminates in dehydration and cardiovascular collapse within the first two weeks of life [179–181]. Although fetal development proceeds normally, these animals present during the first postnatal week with features analogous to pseudo-hypoaldosteronism—marked by hyponatremia, hyperkalemia, growth failure, and markedly elevated plasma renin activity [179, 180]. Mechanistically, the absence of MR impairs epithelial sodium channel (ENaC) function in both the kidney and colon, leading to an approximately eight-fold increase in urinary sodium excretion [179]. Without intervention, such as sodium supplementation, this dysregulation rapidly progresses to hypovolemia and early cardiovascular failure [180].

GRα and MR regulation of neuronal vulnerability and resilience

GRα and MR exert complementary—yet often opposing—influences on neuronal fate, particularly within stress-sensitive brain regions, such as the hippocampus. During stress, GRα activation promotes neuronal vulnerability by upregulating pro-apoptotic mediators, such as B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax) and tumor suppressor p53, while downregulating anti-apoptotic proteins, including Bcl-2 and Bcl-2-like protein 1 (BCL2L1) [165, 166]. In contrast, MR activation enhances neuronal resilience by inducing anti-apoptotic gene expression, maintaining neuronal excitability, and promoting adult neurogenesis, even under basal glucocorticoid concentrations [167, 168]. These neuroprotective effects are most pronounced in the dentate gyrus and CA1 regions of the hippocampus, where MR signaling preserves synaptic architecture and supports adaptive behavior.

While MR confers neuroprotection under baseline conditions, it also modulates GRα responsiveness to excitotoxic and oxidative stress [169]. Specifically, MR-induced FKBP5 expression buffers GRα activity during cellular stress, preserving neuronal integrity and reducing damage vulnerability in stress-sensitive hippocampal circuits [85].

GRα and MR also operate in a temporally coordinated sequence during stress responses: MR governs the initial threat appraisal and facilitates behavioral adaptation, whereas GRα predominates during the recovery phase, promoting systemic recalibration and emotional memory consolidation. Disruption of this sequential coordination, whether through chronic GRα overactivation or MR deficiency, impairs emotional regulation and weakens cognitive resilience [163, 182].

Age-dependent regulation and genetic variability in corticosteroid receptor signaling

Emerging research highlights the functional interdependence of GRα and MR across diverse tissues. MR activity predominates under baseline conditions, sustaining neuronal excitability and promoting anti-apoptotic gene expression, whereas GRα becomes dominant during stress, coordinating recovery and systemic adaptation [83, 145]. This reciprocal pattern acts as a dynamic regulatory switch that allows the brain to alternate between stability and adaptation in response to changing physiological demands. Disruption of this balance, through chronic GRα overactivation or MR deficiency, increases vulnerability to stress-related disorders, including anxiety, depression, and hippocampal atrophy [84, 146].

Moreover, MR indirectly modulates GRα activity via regulation of FKBP5, a molecular chaperone that constrains GRα signaling and limits transcriptional overactivation during stress [85]. The MR-FKBP5-GRα axis serves as a molecular safeguard that buffers against maladaptive gene expression responses during prolonged or repeated glucocorticoid exposure. In parallel, GRα and MR jointly regulate mitochondrial function and oxidative metabolism, ensuring adequate energy availability for both neuronal and systemic demands during stress. Collectively, these findings support a model in which GRα and MR operate as a coordinated regulatory network, with balanced receptor interplay—rather than dominance—governing stress resilience and neuroendocrine homeostasis.

Ultimately, age-related changes in GRα and MR expression profoundly influence neuronal sensitivity, particularly within neural precursor cell populations. With advancing age, GRα expression generally increases while MR expression declines across multiple brain regions, shifting the GRα/MR ratio and heightening neuronal susceptibility to glucocorticoid-induced injury. These receptor shifts modulate critical neurophysiological processes—including stress responsiveness, adult neurogenesis, and synaptic integration—throughout the aging trajectory. Additionally, polymorphic variants in the genes encoding GRα (*NR3C1*) and MR (*NR3C2*) contribute to individual differences in stress vulnerability, neuropsychiatric risk, and broader neurobiological instability [168, 171].

Together, these findings underscore that the resilience or failure of neural and systemic functions is tightly governed by the balance and adaptability of GRα and MR signaling. While age, genetic background, and receptor imbalance heighten vulnerability to neurodegeneration and cognitive decline, growing evidence also links corticosteroid receptor dysfunction to marked immune disturbances.

Loss of MR signaling and the breakdown of immune homeostasis

Loss of MR signaling profoundly disrupts the endocrine-immune integration required to sustain systemic homeostasis. Once regarded primarily as a regulator of renal electrolyte balance, MR is now recognized as a pivotal mediator of immune competence and tissue stability. Deficiency or dysfunction of MR alters inflammatory tone, macrophage polarization, and cytokine balance, weakening host defense and promoting chronic inflammation. This section examines how impaired MR signaling compromises immune regulation and contributes to the breakdown of systemic homeostatic control.

GRα and MR as immune regulators

GRα is widely recognized for its multifaceted role in immune regulation, functioning as both a modulator and, under certain conditions, a suppressor of immune activity. Under physiological conditions, GRα maintains immune homeostasis by regulating the development, trafficking, apoptosis, and cytokine production of both innate and adaptive immune cells.

Traditionally associated with renal sodium retention, MR has now emerged as a critical immunoregulatory receptor. It influences the differentiation, activation, and survival of immune cells, particularly macrophages and T lymphocytes, and plays a central role in orchestrating inflammatory responses. For instance, MR activation in macrophages promotes a pro-inflammatory M1 phenotype, while its absence favors differentiation toward an anti-inflammatory M2 phenotype [59, 183–185].

Together, GRα and MR act as hormonal gatekeepers of the immune system, integrating endocrine signals with immune signaling. Their coordinated actions govern the magnitude and duration of inflammatory responses in key tissues such as the brain, gut, and vasculature—linking the systemic stress response to the preservation or disruption of immune homeostasis. To contextualize their overlapping yet distinct contributions to immune regulation, Table 4 presents a comparative summary of their systemic functions and the physiological consequences of receptor loss [16, 83–87, 145, 146]. These findings emphasize MR's essential role in coupling endocrine signaling with immune surveillance, inflammatory regulation, and tissue repair.

Table 4. Distinct and overlapping functions of GRα and MR: systemic roles and consequences of loss.

GRα—key functions and consequences*	MR—key functions and consequences
Regulates the function of all organs and circulating immune/non-immune cells; master regulator of homeostasis and homeostatic corrections [10, 83].	Sodium and electrolyte homeostasis, including potassium balance and acid-base regulation [87].
Coordinates stress adaptation, metabolism, and mitochondrial function; maintains glucose availability under stress [83, 84].	Blood pressure and vascular tone regulation [16, 86].
Controls immune responses, inflammation resolution, and barrier integrity; protects vascular endothelium via eNOS activation and anti-inflammatory signaling [83, 85].	Macrophage survival and innate immunity [85].
Supports neurodevelopment and brain resilience [145].	Inflammatory regulation and FKBP5 buffering [85].
Integrates systemic communication: vascular, neural, lymphatic; first-line responder to physiological stress [10, 83].	Neuroendocrine modulation under stress [146].
Orchestrates transcriptional and non-genomic signaling responses essential for survival during stress [83].	Loss leads to salt-wasting, vascular inflammation, and localized immune collapse [86].
Loss causes multisystem failure: including neuronal apoptosis, immune collapse, metabolic breakdown [83, 145].	Does not compensate for GRα in systemic regulation; deletion results in regional—not global—physiological failure [86].

*: GRα is the only receptor proven essential for postnatal survival, serving as a master integrator of systemic homeostasis. It coordinates cross-organ communication, linking metabolic, immune, mitochondrial, neurodevelopmental, and vascular–neural–lymphatic functions through both transcriptional and rapid non-genomic pathways. MR, by contrast, governs more localized processes—such as electrolyte balance, vascular tone, and innate immune activity—that, while vital, cannot substitute for GRα's system-wide regulatory role. The table compares their distinct and shared functions, outlining the consequences of receptor loss, including multisystem failure with GRα deletion versus compartmentalized dysfunction with MR deletion. GRα: glucocorticoid receptor alpha; MR: mineralocorticoid receptor; eNOS: endothelial nitric oxide synthase; FKBP5: FK506 binding protein 5.

Cellular effects of MR signaling in immune homeostasis

Building on the immunomodulatory roles outlined in Immune collapse: the role of MR in immune competence and GR-MR interdependence: a unified axis of stress regulation and survival, this section examines additional mechanistic layers that define how MR influences immune cell function under both physiological and pathological conditions. In immune populations—including macrophages, monocytes, T cells, and B lymphocytes—MR signaling exerts cell type-specific regulatory effects that shape local tissue inflammation and systemic immune balance. In macrophages, MR signaling not only encourages polarization toward a pro-inflammatory M1 phenotype but also regulates downstream effector pathways, including oxidative burst capacity, inflammasome activation, and matrix-remodeling enzyme production—thereby amplifying innate immune responses [86, 148]. In T lymphocytes, MR extends its influence beyond Th1 and Th17 differentiation by modulating immunometabolic reprogramming. It promotes glycolysis-dependent proliferation and cytokine production, sustaining effector function during inflammatory challenges [16, 86].

Loss or pharmacologic blockade of MR disrupts these transcriptional and metabolic programs, leading to dysregulated immune responses, impaired pathogen clearance, and increased tissue injury in organ systems such as the kidney, vasculature, and heart [16, 150]. Collectively, these findings position MR as a context-dependent amplifier of immune activation, dynamically coordinating innate and adaptive responses to preserve immune homeostasis under stress and disease conditions.

MR overactivation in disease: a pathway to chronic inflammation

Building on earlier discussions (Immune collapse: the role of MR in immune competence and GR-MR interdependence: a unified axis of stress regulation and survival), pathological MR overactivation functions as a systemic inflammatory amplifier, driving disease progression across cardiovascular, renal, and immune systems. The same receptor that supports immune competence under normal conditions becomes maladaptive in chronic disease states—driving tissue injury, ECM accumulation, and immune dysregulation.

In cardiovascular tissues, excessive MR signaling enhances pro-inflammatory cascades, stimulates collagen synthesis, and accelerates fibrotic remodeling—contributing to the pathogenesis of atherosclerosis, vascular stiffness, and heart failure [148, 149, 186, 187]. In renal tissues, sustained MR activation triggers macrophage-driven inflammation and fibrosis, exacerbating chronic kidney disease and impairing repair mechanisms [16, 86, 150, 188]. Pharmacologic MR antagonism mitigates these pathological processes by reducing immune cell infiltration, suppressing cytokine production, and preserving tissue structure and function [151, 189]. Besides damaging individual organs, overactive MR signaling disrupts immune equilibrium by driving macrophage polarization toward the pro-inflammatory M1 state and away from the anti-inflammatory M2 phenotype, while simultaneously promoting T helper cell differentiation into Th1 and Th17 lineages. This sustained pro-inflammatory bias propagates chronic inflammation and diminishes the immune system's capacity to tolerate harmless stimuli or achieve resolution [184].

Collectively, these findings underscore the growing clinical relevance of MR antagonists in cardiovascular, renal, and inflammatory diseases. Their capacity to suppress inflammation, limit ECM accumulation, and preserve tissue architecture highlights the translational importance of therapeutically targeting the MR axis [150].

Cardiometabolic consequences of MR dysregulation

As discussed in Loss of MR signaling and the breakdown of immune homeostasis, MR overactivation contributes to cardiovascular and renal inflammation. This section expands this framework to encompass the broader cardiometabolic network, showing how persistent MR dysregulation drives systemic metabolic decline. Under physiological conditions, MR coordinates vascular tone, fluid balance, and energy metabolism. However, with aging, metabolic stress, or hormonal excess, its signaling shifts from adaptive to pathogenic—linking vascular inflammation, myocardial remodeling, and adipose tissue dysfunction into a unified process of cardiometabolic deterioration.

MR overactivation and cardiometabolic decline

As expanded from Disruption of cardiometabolic homeostasis and MR overactivation in disease: a pathway to chronic inflammation, sustained MR overactivation contributes to cardiovascular and metabolic pathology through converging mechanisms that include endothelial dysfunction, myocardial fibrosis, and chronic inflammation. These maladaptive pathways intensify with aging and persistent metabolic stress, positioning MR as a central driver of progressive cardiometabolic decline [150, 151].

Beyond its vascular and myocardial effects, MR exerts a far-reaching influence on metabolic tissues. In adipose depots, excessive MR signaling promotes visceral fat accumulation, reduces insulin sensitivity, and alters adipokine secretion—particularly through dysregulation of leptin and resistin—thereby amplifying systemic metabolic dysfunction [158, 159]. In parallel, MR-driven oxidative stress and ECM deposition accelerate atherogenesis, valvular stiffening, and calcification [155, 156].

In contrast, MR antagonists have been shown to lower blood pressure, reduce cardiac fibrosis, and improve glycemic control—underscoring their therapeutic value in the integrated management of cardiovascular and metabolic disease [150, 151].

Receptor diversity and functional crosstalk in glucocorticoid signaling

As outlined in Cardiometabolic consequences of MR dysregulation, MR overactivation highlights how disruption of a single corticosteroid receptor can propagate inflammation and oxidative injury across cardiovascular, metabolic, and immune systems. Extending this systems perspective, this section explores receptor diversity and functional crosstalk within the glucocorticoid signaling network, focusing on GRα's uniquely non-redundant role in maintaining systemic adaptation and survival.

Phenotypic evidence for GRα non-redundancy

The NR superfamily regulates a wide range of essential physiological processes, including metabolism, immunity, development, and stress adaptation. Within this family, GRα is uniquely indispensable. Unlike other NRs—such as PPARγ, RAR, and ERα—GRα orchestrates an integrative response across immune, metabolic, and neural systems, ensuring dynamic homeostatic correction during physiological stress. No other receptors can substitute for this systemic role.

Phenotypic studies in knockout models confirm this non-redundancy. Complete GRα deletion produces perinatal lethality and multisystem failure, characterized by neuronal apoptosis, immune collapse, hypoglycemia, and cardiovascular dysfunction [130, 132, 135, 190]. In contrast, deletion of other NRs results in tissue-specific deficits or phenotypes that can be compensated for through alternative developmental pathways. Even NRs with partial transcriptional overlap fail to restore systemic equilibrium in the absence of GRα.

GRα therefore functions as a regulatory keystone—more than a single effector, it is the integrator of organismal survival and systemic stability. Its loss precipitates a cascade of interdependent failures across neural, immune, metabolic, and vascular systems, culminating in systemic collapse.

Functional asymmetry within nuclear receptor networks

Mapping the NR landscape reveals a central organizing principle: systemic regulation depends on functional hierarchy rather than redundancy. Although GRα engages in extensive crosstalk with other NRs, none can replicate its integrative control under physiological stress or immune activation.

Receptors such as PPARα and ERα may modulate subsets of GRα-responsive genes; however, they lack the rapid activation kinetics, breadth of transcriptional targets, and across-tissues versatility that define GRα. Through both genomic and non-genomic signaling, GRα coordinates immune, metabolic, and vascular responses within minutes of glucocorticoid exposure. In vivo, loss of any other single NR fails to reproduce the systemic collapse and multi-organ failure observed with GRα deficiency [130, 132, 135, 190]. Thus, while NR crosstalk adds regulatory nuance and fine-tuning, GRα remains the central integrator that imparts coherence, hierarchy, and directionality to the entire NR network.

Mechanisms of nuclear receptor crosstalk: non-redundancy of GRα

NR crosstalk expands transcriptional flexibility through mechanisms such as heterodimerization (the pairing of two different receptors that bind DNA together to regulate shared target genes), cofactor competition, and reciprocal transcriptional modulation (where receptors mutually enhance or suppress each other's gene expression depending on context). However, these interactions do not create functional redundancy for GRα, whose systemic regulatory roles remain distinct and irreplaceable.

GRα forms heterodimers with partners such as PPARγ and LXRs, thereby broadening its transcriptional reach but not diminishing its centrality. These heterodimers depend on GRα for activation, not the reverse [131, 191]. Likewise, GRα can cross-regulate other NRs, including PPARγ and ERα, but this influence is largely unidirectional: loss of GRα disrupts multiple physiological systems, whereas loss of other NRs does not produce a comparable systemic collapse [192, 193].

GRα also competes for shared coregulators such as RXR and common coactivators (e.g., PPARs, thyroid hormone receptors), typically dominating these interactions during stress-induced transcription [194, 195]. Even under pharmacologic stimulation, PPAR agonists fail to rescue immune or metabolic dysfunction in GRα-deficient models, further underscoring its non-substitutable role [131, 196].

In summary, although NR crosstalk refines transcriptional networks, it does not establish redundancy. GRα remains uniquely indispensable—the central coordinator of systemic homeostasis and stress resilience.

Non-genomic actions of GRα in rapid stress and immune adaptation

Building on Receptor diversity and functional crosstalk in glucocorticoid signaling, which examined the diversity and crosstalk of NRs in genomic regulation, this section shifts focus to the rapid, non-genomic actions of GRα that complement its transcriptional control. While genomic signaling orchestrates long-term homeostatic adjustments, non-genomic GRα mechanisms provide immediate physiological stabilization during acute stress. These actions, triggered within seconds to minutes of glucocorticoid exposure, arise from membrane-associated, cytoplasmic, and mitochondrial GRα pools that modulate vascular tone, mitochondrial energy flux, and inflammatory signaling. Together, these rapid responses bridge the temporal gap between acute stress adaptation and slower genomic regulation, ensuring system integrity when rapid restoration of homeostasis is most critical.

Beyond transcription: overview of non-genomic GRα functions

Although GRα is traditionally recognized for its role in genomic regulation as a nuclear transcription factor, accumulating evidence highlights its essential non-genomic functions, particularly during acute physiological stress. These rapid actions occur within minutes of ligand binding and are mediated through cytoplasmic, mitochondrial, and membrane-associated pathways, entirely independent of direct gene transcription [6]. Through these mechanisms, GRα can rapidly modulate immune cell activity, glucose metabolism, and mitochondrial function—processes critical for sustaining the body's immediate response to stress or injury.

Such non-genomic pathways are particularly significant in critical illness, where rapid correction of immune and metabolic imbalances can determine survival outcomes. Impaired GRα activity—often worsened by energy depletion, oxidative stress, and micronutrient deficiencies—has been strongly linked to a poorer clinical prognosis. Conversely, therapeutic strategies that enhance GRα signaling and restore metabolic reserves may improve outcomes in critically ill patients [6]. Collectively, non-genomic GRα signaling forms as a cornerstone of early physiological adaptation, orchestrating rapid responses during acute stress, immune activation, and metabolic disruption. The specific cellular mechanisms underlying these responses—including immune redistribution, glucose mobilization, and mitochondrial stabilization—are examined in detail in Multisystem deployment: immune, metabolic, and mitochondrial stabilization.

Multisystem deployment: immune, metabolic, and mitochondrial stabilization

Beyond its transcription-independent activation, GRα plays a central role in coordinating immune redistribution and metabolic resource allocation during the early phases of stress. Within minutes of glucocorticoid exposure, GRα rapidly directs immune cell trafficking to sites of injury or infection and stimulates glucose mobilization—facilitating tissue readiness without reliance on genomic signaling [197]. These rapid adaptations enhance frontline defense capacity while reallocating energy resources to meet acute physiological demands.

Concurrently, GRα localizes to mitochondrial membranes, where it preserves membrane potential, regulates calcium buffering, and prevents opening of the mitochondrial permeability transition pore (mPTP), a critical trigger of apoptosis [198]. By stabilizing mitochondrial function, GRα sustains ATP production, limits oxidative stress, and protects metabolically active tissues from collapse. Together, these non-genomic GRα mechanisms deliver immediate multisystem resilience, linking endocrine stress signals to cellular survival pathways, and bridging the transition from acute response to longer-term genomic regulation [197].

Neuroendocrine and vascular adaptation under acute stress

In the CNS, GRα extends beyond the nucleus, localizing to synapses, the cytoplasm, and plasma membranes of both neurons and astrocytes. This strategic distribution enables rapid non-genomic signaling that modulates glutamatergic transmission, receptor trafficking, and neuronal excitability through kinase pathways, such as MAPK and PI3K/Akt. These fast-acting mechanisms shape acute behavioral responses to stress and facilitate neuroplastic adaptation within stress-reactive circuits [199, 200].

Concurrently, GRα exerts critical non-genomic effects on vascular adaptation, particularly during systemic inflammation. It activates endothelial nitric oxide synthase (eNOS), increases nitric oxide bioavailability, reduces leukocyte-endothelial adhesion, and preserves endothelial barrier integrity. These actions support perfusion and limit inflammatory injury in critically ill patients [124]. In summary, GRα's non-genomic actions in the nervous and vascular systems act in concert to preserve neural function, maintain perfusion, and protect vascular integrity—ensuring coordinated systemic adaptation during acute stress (Table 5).

Table 5. Phases of non-genomic corticosteroid action.

Phase	Mechanism/Target	Time scale	Key features
Immediate membrane effects [201, 202, 205].	Interaction with membrane components, aquaporins (AQPs), or membrane-associated GRα/MR	Seconds–minutes	Rapid ion/signaling changes
Secondary intracellular [201, 203].	PI3K/Akt, Ca^{2+} pathways; caveolin-1 scaffolding	Minutes	Non-transcriptional signaling
Integration with genomic [201, 203, 204].	Nuclear MR/GR, gene expression	15+ minutes	Priming for genomic effects

This table summarizes the sequential phases of rapid, transcription-independent corticosteroid signaling. Immediate membrane effects occur within seconds to minutes, followed by intracellular signaling cascades within minutes, and integration with genomic actions at 15 minutes or longer. See A phasic model of GRα non-genomic stress response for a detailed description. GRα: glucocorticoid receptor alpha; MR: mineralocorticoid receptor.

These rapid, transcription-independent mechanisms can be synthesized into a phased model that outlines the temporal sequence of non-genomic corticosteroid actions. In the immediate membrane phase, corticosteroids interact with cell membranes and putative membrane receptors, including aquaporins, ion channels, and membrane-associated GR/MR, rapidly altering ion fluxes and intracellular signaling within minutes [201, 202]. In the secondary intracellular signaling phase, during which the membrane interactions activate PI3K/Akt and Ca^{2+} mobilization, modulating vascular tone, mitochondrial stability, and immune activation [201, 203]. Finally, in the integration phase, these rapid response prime cells for slower genomic effects through nuclear GR/MR interactions, aligning immediate buffering with longer-term transcriptional adaptation [201, 204].

This phased sequence provides the mechanistic foundation for the broader model of GRα-mediated non-genomic stress response. Building on the mechanistic framework, Table 4 integrates these findings, highlighting the systemic indispensability of GRα in contrast to the tissue-specific functions of MR and the distinct consequences that arise from their imbalance.

A phasic model of GRα non-genomic stress response

Taken together, the non-genomic functions of GRα unfold in a structured, phasic sequence that links cellular events with systemic functional outcomes.

At the mechanistic level (Table 5) [201–203, 205], non-genomic corticosteroid signaling begins with the immediate membrane phase, where GRα and MR interact with membrane components—including aquaporins, ion channels, or membrane-associated receptors—initiating rapid ion fluxes and signaling changes within seconds to minutes [201–205]. This is followed by the secondary intracellular signaling phase, where these membrane interactions activate PI3K/Akt and Ca^{2+} pathways via scaffolding proteins such as caveolin-1, thereby stabilizing vascular tone, mitochondrial function, and immune activation [201, 203]. Finally, in the integration phase, occurring within 15 minutes or more, these rapid cascades prime nuclear GR/MR interactions and gene transcription, forming a bridge between fast, cytoplasmic signaling and slower, genomic adaptation [201, 203, 204].

At the systemic level, these mechanistic phases correspond to broader functional outcomes. During the priming phase, GRα rapidly mobilizes energy stores and directs immune cells. In the modulatory phase, it stabilizes mitochondrial and vascular functions, preserving cellular integrity and systemic perfusion. Finally, in the restorative phase, GRα initiates early tissue repair and pro-resolving inflammatory signals—even before genomic pathways are fully engaged [6].

This multi-level organization demonstrates how rapid membrane and intracellular mechanisms (seconds to minutes) serve as a biological first responder, providing an immediate buffer that sustains perfusion, vascular integrity, and immune readiness while preparing the transition to genomic recovery. By maintaining cell viability and systemic stability across both mechanistic and functional domains, GRα's non-genomic signaling emerges not as ancillary but as an essential arm of glucocorticoid-mediated survival.

Collectively, these findings confirm that GRα's non-genomic actions are crucial for survival during acute physiological stress. Through its integrated effects on membranes, mitochondria, and cytoplasm, GRα rapidly coordinates immune response, vascular tone, and cellular stability—underscoring its unique role in maintaining systemic balance and ensuring survival during critical illness.

Conclusions

From conception through fetal development and across the lifespan, GRα functions as the master regulator of systemic homeostasis. Beyond its classical role in stress adaptation, GRα coordinates the development and function of virtually every tissue, circulating cell population, and organ system, integrating neural, vascular, immune, metabolic, and lymphatic networks. Its signaling enables rapid, bidirectional communication across these systems, mediating swift physiological responses to internal and external challenges. This integrative control is not merely modulatory but foundational, sustaining homeostatic balance and activating corrective mechanisms whenever equilibrium is threatened. GRα thus emerges not only as a mediator of stress but as an indispensable survival receptor (Table 1) [6, 19–49].

Its unique ability to activate both genomic and non-genomic pathways across diverse tissues explains its capacity to preserve life under acute stress. Experimental evidence from genetic knockout and pharmacological models confirms that GRα deletion results in multisystem failure—characterized by neuronal apoptosis, immune collapse, cardiovascular breakdown, and metabolic instability. In contrast, disruption of other NRs typically produces localized or compensatory dysfunctions. Remarkably, murine models lacking GR's DNA-binding domain can survive, indicating that non-genomic GRα signaling alone is sufficient to sustain postnatal viability [122].

Critically, the GRα function is not autonomous. It is dependent on systemic inputs, including micronutrient status, microbiome composition, and bioenergetic and metabolic resilience. Trace elements and minerals (such as zinc, magnesium, and selenium), together with vitamins (such as A, D, and B-complex) and microbial metabolites, modulate GRα expression, nuclear translocation, and downstream signaling [206]. Dysbiosis [58], oxidative stress, malnutrition, or micronutrient deficiency (common in critically ill patients) can significantly impair GRα function, reducing the organism's capacity to sustain energy production and mount adaptive responses to physiological stress or inflammation. Thus, GRα operates at the nexus of endocrine, nutritional, and microbial regulation—serving both as a central integrator of systemic control and a critical point of vulnerability when disrupted.

This reconceptualization of GRα as a core survival receptor—essential throughout development and adult physiology—demands a paradigm shift in translational medicine. Historically, the underappreciation of GRα's integrated genomic and non-genomic functions and its central role in each phase of homeostatic corrections has slowed progress in treating critical illnesses, corticosteroid resistance, and systemic inflammatory disorders. Future approaches should focus on preserving or restoring GRα signaling—both its genomic and non-genomic pathways—as a unified therapeutic strategy to stabilize homeostasis and improve outcomes in acute and chronic diseases.

In summary, GRα is not merely a stress-response receptor but a central integrative axis of survival—embedded within a broader network of nutritional, microbial, and metabolic systems that regulate energy balance, redox homeostasis, and adaptive resilience. In this light, GRα can be viewed as a biological counterpart to the so-called "*God particle*"—not just metaphorically, but as a systems-level integrator whose dysfunction disrupts coordinated physiological regulation. Its role is not ancillary, but foundational, supporting survival across immune, metabolic, cardiovascular, and neuroendocrine systems. The breakdown of this receptor's function marks the critical inflection point where adaptation gives way to systemic collapse. Restoring and preserving GRα function represents a unifying frontier in medicine—offering a pathway to reestablish homeostasis in critical illness and enhance resilience across acute, chronic, degenerative, and age-related conditions.

Abbreviations

AMPK: adenosine monophosphate-activated protein kinase

ARDS: acute respiratory distress syndrome

Bcl-2: B-cell lymphoma 2

CNS: central nervous system

ECM: extracellular matrix

ERα: estrogen receptor alpha

FKBP5: FK506-binding protein 5

GPCRs: G protein-coupled receptors

GRE: glucocorticoid response element

GRα: glucocorticoid receptor alpha

HPA: hypothalamic-pituitary-adrenal

HTR2C: 5-HT_2C receptor

IL-1R: interleukin-1 receptor

MR: mineralocorticoid receptor

NF-κB: nuclear factor kappa B

NMDA: *N*-methyl-*D*-aspartate

NRs: nuclear receptors

phospho-AMPK: phosphorylated AMP-activated protein kinase

PPARα: peroxisome proliferator-activated receptor alpha

RIPK1: receptor-interacting protein kinase 1

TLRs: Toll-like receptors

Declarations

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References

1. Cannon W. The wisdom of the body. New York: W. W. Norton & Company, Inc.; 1929. pp. 399–431.
2. SELYE H. The general adaptation syndrome and the diseases of adaptation. J Clin Endocrinol Metab. 1946;6:117–230. [DOI] [PubMed]
3. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason J, editors. Handbook of life stress, cognition and health. New York: John Wiley & Sons; 1988. pp. 629–49.
4. Sterling P. Allostasis: a model of predictive regulation. Physiol Behav. 2012;106:5–15. [DOI] [PubMed]
5. Billman GE. Homeostasis: The Underappreciated and Far Too Often Ignored Central Organizing Principle of Physiology. Front Physiol. 2020;11:200. [DOI] [PubMed] [PMC]
6. Meduri G. Glucocorticoid receptor alpha: origins and functions of the master regulator of homeostatic corrections in health and critical illness. Explor Endocr Metab Dis. 2025;2:101426. [DOI]
7. Reichardt HM, Kaestner KH, Tuckermann J, Kretz O, Wessely O, Bock R, et al. DNA binding of the glucocorticoid receptor is not essential for survival. Cell. 1998;93:531–41. [DOI] [PubMed]
8. Faught E, Schaaf MJM. The Mineralocorticoid Receptor Plays a Crucial Role in Macrophage Development and Function. Endocrinology. 2023;164:bqad127. [DOI] [PubMed] [PMC]
9. Kawano SM, Blob RW. Propulsive forces of mudskipper fins and salamander limbs during terrestrial locomotion: implications for the invasion of land. Integr Comp Biol. 2013;53:283–94. [DOI] [PubMed]
10. Meduri GU, Psarra AG. The Glucocorticoid System: A Multifaceted Regulator of Mitochondrial Function, Endothelial Homeostasis, and Intestinal Barrier Integrity. Semin Respir Crit Care Med. 2025;[Epub ahead of print]. [DOI] [PubMed]
11. Kokkinopoulou I, Moutsatsou P. Mitochondrial Glucocorticoid Receptors and Their Actions. Int J Mol Sci. 2021;22:6054. [DOI] [PubMed] [PMC]
12. Morgan DJ, Poolman TM, Williamson AJK, Wang Z, Clark NR, Ma'ayan A, et al. Glucocorticoid receptor isoforms direct distinct mitochondrial programs to regulate ATP production. Sci Rep. 2016;6:26419. [DOI] [PubMed] [PMC]
13. Du J, Wang Y, Hunter R, Wei Y, Blumenthal R, Falke C, et al. Dynamic regulation of mitochondrial function by glucocorticoids. Proc Natl Acad Sci U S A. 2009;106:3543–8. [DOI] [PubMed] [PMC]
14. Choi GE, Han HJ. Glucocorticoid impairs mitochondrial quality control in neurons. Neurobiol Dis. 2021;152:105301. [DOI] [PubMed]
15. Lapp HE, Bartlett AA, Hunter RG. Stress and glucocorticoid receptor regulation of mitochondrial gene expression. J Mol Endocrinol. 2019;62:R121–8. [DOI] [PubMed]
16. Belden Z, Deiuliis JA, Dobre M, Rajagopalan S. The Role of the Mineralocorticoid Receptor in Inflammation: Focus on Kidney and Vasculature. Am J Nephrol. 2017;46:298–314. [DOI] [PubMed] [PMC]
17. Quagliarini F, Makris K, Friano ME, Uhlenhaut NH. EJE Prize 2023: genes on steroids-genomic control of hepatic metabolism by the glucocorticoid receptor. Eur J Endocrinol. 2023;188:R111–30. [DOI] [PubMed]
18. Faught E, Schaaf MJM. Molecular mechanisms of the stress-induced regulation of the inflammatory response in fish. Gen Comp Endocrinol. 2024;345:114387. [DOI] [PubMed]
19. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. J Allergy Clin Immunol. 2013;132:1033–44. [DOI] [PubMed] [PMC]
20. Ayroldi E, Riccardi C. Glucocorticoid-induced leucine zipper (GILZ): a new important mediator of glucocorticoid action. FASEB J. 2009;23:3649–58. [DOI] [PubMed]
21. Baschant U, Tuckermann J. The role of the glucocorticoid receptor in inflammation and immunity. J Steroid Biochem Mol Biol. 2010;120:69–75. [DOI] [PubMed]

22. Lannan EA, Galliher-Beckley AJ, Scoltock AB, Cidlowski JA. Proinflammatory actions of glucocorticoids: glucocorticoids and TNFα coregulate gene expression in vitro and in vivo. Endocrinology. 2012;153:3701–12. [DOI] [PubMed] [PMC]
23. González-Mayoral A, Eid A, Derounian R, Campanella VS, da Silva Ramos A, El Khoury R, et al. Mineralocorticoid receptor knockout in Schwann cells alters myelin sheath thickness. J Endocrinol. 2023;258:e220334. [DOI] [PubMed]
24. Abrahám I, Harkany T, Horvath KM, Veenema AH, Penke B, Nyakas C, et al. Chronic corticosterone administration dose-dependently modulates Abeta(1-42)- and NMDA-induced neurodegeneration in rat magnocellular nucleus basalis. J Neuroendocrinol. 2000;12:486–94. [DOI] [PubMed]
25. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol. 2005; 67:259–84. [DOI] [PubMed]
26. Yang S, Zhang L. Glucocorticoids and vascular reactivity. Curr Vasc Pharmacol. 2004;2:1–12. [DOI] [PubMed]
27. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21: 55–89. [DOI] [PubMed]
28. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev. 2007;87:873–904. [DOI] [PubMed]
29. Bouazza Y, Sennoun N, Strub C, Regnault V, Gibot S, Meziani F, et al. Comparative effects of recombinant human activated protein C and dexamethasone in experimental septic shock. Intensive Care Med. 2011;37:1857–64. [DOI] [PubMed]
30. Limbourg FP, Huang Z, Plumier JC, Simoncini T, Fujioka M, Tuckermann J, et al. Rapid nontranscriptional activation of endothelial nitric oxide synthase mediates increased cerebral blood flow and stroke protection by corticosteroids. J Clin Invest. 2002;110:1729–38. [DOI] [PubMed] [PMC]
31. Hafezi-Moghadam A, Simoncini T, Yang Z, Limbourg FP, Plumier J, Rebsamen MC, et al. Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase. Nat Med. 2002;8:473–9. [DOI] [PubMed] [PMC]
32. Gaeggeler HP, Gonzalez-Rodriguez E, Jaeger NF, Loffing-Cueni D, Norregaard R, Loffing J, et al. Mineralocorticoid versus glucocorticoid receptor occupancy mediating aldosterone-stimulated sodium transport in a novel renal cell line. J Am Soc Nephrol. 2005;16:878–91. [DOI] [PubMed]
33. Goleva E, Jackson LP, Gleason M, Leung DYM. Usefulness of PBMCs to predict clinical response to corticosteroids in asthmatic patients. J Allergy Clin Immunol. 2012;129:687–93. [DOI] [PubMed] [PMC]
34. Yang HH, Su SH, Ho CH, Yeh AH, Lin YJ, Yu MJ. Glucocorticoid Receptor Maintains Vasopressin Responses in Kidney Collecting Duct Cells. Front Physiol. 2022;13:816959. [DOI] [PubMed] [PMC]
35. Okun JG, Conway S, Schmidt KV, Schumacher J, Wang X, de Guia R, et al. Molecular regulation of urea cycle function by the liver glucocorticoid receptor. Mol Metab. 2015;4:732–40. [DOI] [PubMed] [PMC]
36. Przybyciński J, Drożdżal S, Domański L, Dziedziejko V, Pawlik A. Role of Endothelial Glucocorticoid Receptor in the Pathogenesis of Kidney Diseases. Int J Mol Sci. 2021;22:13295. [DOI] [PubMed] [PMC]
37. Jenniskens M, Weckx R, Dufour T, Vander Perre S, Pauwels L, Derde S, et al. The Hepatic Glucocorticoid Receptor Is Crucial for Cortisol Homeostasis and Sepsis Survival in Humans and Male Mice. Endocrinology. 2018;159:2790–802. [DOI] [PubMed]
38. Kaminsky LW, Al-Sadi R, Ma TY. IL-1β and the Intestinal Epithelial Tight Junction Barrier. Front Immunol. 2021;12:767456. [DOI] [PubMed] [PMC]
39. Reichardt SD, Amouret A, Muzzi C, Vettorazzi S, Tuckermann JP, Lühder F, et al. The Role of Glucocorticoids in Inflammatory Diseases. Cells. 2021;10:2921. [DOI] [PubMed] [PMC]

40. Huang EY, Inoue T, Leone VA, Dalal S, Touw K, Wang Y, et al. Using corticosteroids to reshape the gut microbiome: implications for inflammatory bowel diseases. Inflamm Bowel Dis. 2015;21:963–72. [DOI] [PubMed] [PMC]
41. Sen SK, Wang L, Brown M, Wu J, Wei Z, Matveyenko A. 1773-P: Glucocorticoid Receptor Signaling Regulates Pancreatic Beta-Cell Circadian Transcriptome and Function. Diabetes. 2023;72:1773. [DOI]
42. Aylward A, Okino ML, Benaglio P, Chiou J, Beebe E, Padilla JA, et al. Glucocorticoid signaling in pancreatic islets modulates gene regulatory programs and genetic risk of type 2 diabetes. PLoS Genet. 2021;17:e1009531. [DOI] [PubMed] [PMC]
43. Swali A, Walker EA, Lavery GG, Tomlinson JW, Stewart PM. 11beta-Hydroxysteroid dehydrogenase type 1 regulates insulin and glucagon secretion in pancreatic islets. Diabetologia. 2008;51:2003–11. [DOI] [PubMed]
44. Shen Y, Roh HC, Kumari M, Rosen ED. Adipocyte glucocorticoid receptor is important in lipolysis and insulin resistance due to exogenous steroids, but not insulin resistance caused by high fat feeding. Mol Metab. 2017;6:1150–60. [DOI] [PubMed] [PMC]
45. Vali A, Dalle H, Loubaresse A, Gilleron J, Havis E, Garcia M, et al. Adipocyte Glucocorticoid Receptor Activation With High Glucocorticoid Doses Impairs Healthy Adipose Tissue Expansion by Repressing Angiogenesis. Diabetes. 2024;73:211–24. [DOI] [PubMed]
46. Dalle H, Garcia M, Antoine B, Boehm V, Do TTH, Buyse M, et al. Adipocyte Glucocorticoid Receptor Deficiency Promotes Adipose Tissue Expandability and Improves the Metabolic Profile Under Corticosterone Exposure. Diabetes. 2019;68:305–17. [DOI] [PubMed]
47. Du X, Xu W, Shi J, Guo K, Guo C, Zheng R, et al. Glucocorticoid Receptor Alpha Targets SLC2A4 to Regulate Protein Synthesis and Breakdown in Porcine Skeletal Muscle Cells. Biomolecules. 2021;11: 721. [DOI] [PubMed] [PMC]
48. Kuo T, Harris CA, Wang JC. Metabolic functions of glucocorticoid receptor in skeletal muscle. Mol Cell Endocrinol. 2013;380:79–88. [DOI] [PubMed] [PMC]
49. Wang SCM, Myers S, Dooms C, Capon R, Muscat GEO. An ERRbeta/gamma agonist modulates GRalpha expression, and glucocorticoid responsive gene expression in skeletal muscle cells. Mol Cell Endocrinol. 2010;315:146–52. [DOI] [PubMed]
50. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, et al. Critical Illness-Related Corticosteroid Insufficiency (CIRCI): A Narrative Review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Crit Care Med. 2017;45:2089–98. [DOI] [PubMed]
51. Meduri GU, Confalonieri M, Chaudhuri D, Rochwerg B, Meibohm B. Prolonged glucocorticoid treatment in ARDS: pathobiological rationale and pharmacological principles. In: Fink G, editor. Handbook of Stress: Stress, Immunology and Inflammation. Academic Press; 2024. pp. 289–323. [DOI]
52. Lu NZ, Cidlowski JA. The origin and functions of multiple human glucocorticoid receptor isoforms. Ann N Y Acad Sci. 2004;1024:102–23. [DOI] [PubMed]
53. Sacta MA, Chinenov Y, Rogatsky I. Glucocorticoid Signaling: An Update from a Genomic Perspective. Annu Rev Physiol. 2016;78:155–80. [DOI] [PubMed]
54. Kino T, Su YA, Chrousos GP. Human glucocorticoid receptor isoform beta: recent understanding of its potential implications in physiology and pathophysiology. Cell Mol Life Sci. 2009;66:3435–48. [DOI] [PubMed] [PMC]
55. Rodriguez JM, Monsalves-Alvarez M, Henriquez S, Llanos MN, Troncoso R. Glucocorticoid resistance in chronic diseases. Steroids. 2016;115:182–92. [DOI] [PubMed]
56. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet. 2009;373: 1905–17. [DOI] [PubMed]

57. Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc Natl Acad Sci U S A. 2012; 109:5995–9. [DOI] [PubMed] [PMC]
58. Meduri GU. Synergistic glucocorticoids, vitamins, and microbiome strategies for gut protection in critical illness. Explor Endocr Metab Dis. 2025;2:101432. [DOI]
59. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17:233–47. [DOI] [PubMed] [PMC]
60. Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther. 2002;96:23–43. [DOI] [PubMed]
61. Meduri GU, Chrousos GP. General Adaptation in Critical Illness: Glucocorticoid Receptor-alpha Master Regulator of Homeostatic Corrections. Front Endocrinol (Lausanne). 2020;11:161. [DOI] [PubMed] [PMC]
62. Meduri GU, Muthiah MP, Carratu P, Eltorky M, Chrousos GP. Nuclear factor-kappaB- and glucocorticoid receptor alpha-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. Neuroimmunomodulation. 2005;12:321–38. [DOI] [PubMed]
63. Vassilatis DK, Hohmann JG, Zeng H, Li F, Ranchalis JE, Mortrud MT, et al. The G protein-coupled receptor repertoires of human and mouse. Proc Natl Acad Sci U S A. 2003;100:4903–8. [DOI] [PubMed] [PMC]
64. Heng BC, Aubel D, Fussenegger M. An overview of the diverse roles of G-protein coupled receptors (GPCRs) in the pathophysiology of various human diseases. Biotechnol Adv. 2013;31:1676–94. [DOI] [PubMed]
65. Kroning KE, Wang W. Genetically encoded tools for in vivo G-protein-coupled receptor agonist detection at cellular resolution. Clin Transl Med. 2022;12:e1124. [DOI] [PubMed] [PMC]
66. Small KM, McGraw DW, Liggett SB. Pharmacology and physiology of human adrenergic receptor polymorphisms. Annu Rev Pharmacol Toxicol. 2003;43:381–411. [DOI] [PubMed]
67. Barnes NM, Ahern GP, Becamel C, Bockaert J, Camilleri M, Chaumont-Dubel S, et al. International Union of Basic and Clinical Pharmacology. CX. Classification of Receptors for 5-hydroxytryptamine; Pharmacology and Function. Pharmacol Rev. 2021;73:310–520. [DOI] [PubMed] [PMC]
68. Simard M, Rakotoarivelo V, Di Marzo V, Flamand N. Expression and Functions of the CB_2 Receptor in Human Leukocytes. Front Pharmacol. 2022;13:826400. [DOI] [PubMed] [PMC]
69. Maßberg D, Hatt H. Human Olfactory Receptors: Novel Cellular Functions Outside of the Nose. Physiol Rev. 2018;98:1739–63. [DOI] [PubMed]
70. Frigo DE, Bondesson M, Williams C. Nuclear receptors: from molecular mechanisms to therapeutics. Essays Biochem. 2021;65:847–56. [DOI] [PubMed] [PMC]
71. Morales-Perez CL, Noviello CM, Hibbs RE. X-ray structure of the human α4β2 nicotinic receptor. Nature. 2016;538:411–5. [DOI] [PubMed] [PMC]
72. Marzvanyan A, Alhawaj AF. Physiology, Sensory Receptors. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025. [PubMed]
73. Arstila TP, Casrouge A, Baron V, Even J, Kanellopoulos J, Kourilsky P. A direct estimate of the human alphabeta T cell receptor diversity. Science. 1999;286:958–61. [DOI] [PubMed]
74. Bsibsi M, Ravid R, Gveric D, van Noort JM. Broad expression of Toll-like receptors in the human central nervous system. J Neuropathol Exp Neurol. 2002;61:1013–21. [DOI] [PubMed]
75. Colonna M. The biology of TREM receptors. Nat Rev Immunol. 2023;23:580–94. [DOI] [PubMed] [PMC]
76. McMahan CJ, Slack JL, Mosley B, Cosman D, Lupton SD, Brunton LL, et al. A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types. EMBO J. 1991;10: 2821–32. [DOI] [PubMed] [PMC]

77. Sapio MR, Staedtler ES, King DM, Maric D, Jahanipour J, Ghetti A, et al. Analgesic candidate adenosine A 3 receptors are expressed by perineuronal peripheral macrophages in human dorsal root ganglion and spinal cord microglia. Pain. 2024;165:2323–43. [DOI] [PubMed] [PMC]
78. Larhammar D, Blomqvist AG, Yee F, Jazin E, Yoo H, Wahlested C. Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y1 type. J Biol Chem. 1992;267:10935–8. [PubMed]
79. Schlicker E, Feuerstein T. Human presynaptic receptors. Pharmacol Ther. 2017;172:1–21. [DOI] [PubMed]
80. Karnik SS, Unal H, Kemp JR, Tirupula KC, Eguchi S, Vanderheyden PML, et al. International Union of Basic and Clinical Pharmacology. XCIX. Angiotensin Receptors: Interpreters of Pathophysiological Angiotensinergic Stimuli [corrected]. Pharmacol Rev. 2015;67:754–819. [DOI] [PubMed] [PMC]
81. Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol. 2001;167:1–5. [DOI] [PubMed]
82. Shen S, Wang D, Liu H, He X, Cao Y, Chen J, et al. Structural basis for hormone recognition and distinctive Gq protein coupling by the kisspeptin receptor. Cell Rep. 2024;43:114389. [DOI] [PubMed]
83. Sueyoshi T, Petrillo MG, Jewell CM, Bortner CD, Perera L, Xu X, et al. Molecular interactions of glucocorticoid and mineralocorticoid receptors define novel transcription and biological functions. J Biol Chem. 2025;301:108488. [DOI] [PubMed] [PMC]
84. Daskalakis NP, Meijer OC, de Kloet ER. Mineralocorticoid receptor and glucocorticoid receptor work alone and together in cell-type-specific manner: Implications for resilience prediction and targeted therapy. Neurobiol Stress. 2022;18:100455. [DOI] [PubMed] [PMC]
85. Hartmann J, Bajaj T, Klengel C, Chatzinakos C, Ebert T, Dedic N, et al. Mineralocorticoid receptors dampen glucocorticoid receptor sensitivity to stress via regulation of FKBP5. Cell Rep. 2021;35: 109185. [DOI] [PubMed] [PMC]
86. Bene NC, Alcaide P, Wortis HH, Jaffe IZ. Mineralocorticoid receptors in immune cells: emerging role in cardiovascular disease. Steroids. 2014;91:38–45. [DOI] [PubMed] [PMC]
87. Almansa R, Heredia-Rodríguez M, Gomez-Sanchez E, Andaluz-Ojeda D, Iglesias V, Rico L, et al. Transcriptomic correlates of organ failure extent in sepsis. J Infect. 2015;70:445–56. [DOI] [PubMed]
88. Bristow MR, Ginsburg R, Umans V, Fowler M, Minobe W, Rasmussen R, et al. Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. Circ Res. 1986;59:297–309. [DOI] [PubMed]
89. Wei W, Smrcka AV. Subcellular β-Adrenergic Receptor Signaling in Cardiac Physiology and Disease. J Cardiovasc Pharmacol. 2022;80:334–41. [DOI] [PubMed] [PMC]
90. Cole TJ, Blendy JA, Monaghan AP, Krieglstein K, Schmid W, Aguzzi A, et al. Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. Genes Dev. 1995;9:1608–21. [DOI] [PubMed]
91. Planey SL, Litwack G. Glucocorticoid-induced apoptosis in lymphocytes. Biochem Biophys Res Commun. 2000;279:307–12. [DOI] [PubMed]
92. Adams SM, de Rivero Vaccari JC, Corriveau RA. Pronounced cell death in the absence of NMDA receptors in the developing somatosensory thalamus. J Neurosci. 2004;24:9441–50. [DOI] [PubMed] [PMC]
93. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, Dikranian K, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 1999;283:70–4. [DOI] [PubMed]

94. Zhang S, Steijaert MN, Lau D, Schütz G, Delucinge-Vivier C, Descombes P, et al. Decoding NMDA receptor signaling: identification of genomic programs specifying neuronal survival and death. Neuron. 2007;53:549–62. [DOI] [PubMed]

95. Martel MA, Wyllie DJA, Hardingham GE. In developing hippocampal neurons, NR2B-containing *N*-methyl-*D*-aspartate receptors (NMDARs) can mediate signaling to neuronal survival and synaptic potentiation, as well as neuronal death. Neuroscience. 2009;158:334–43. [DOI] [PubMed] [PMC]

96. Wang R, Reddy PH. Role of Glutamate and NMDA Receptors in Alzheimer's Disease. J Alzheimers Dis. 2017;57:1041–8. [DOI] [PubMed] [PMC]

97. Deng R, Chang M, Kao JPY, Kanold PO. Cortical inhibitory but not excitatory synaptic transmission and circuit refinement are altered after the deletion of NMDA receptors during early development. Sci Rep. 2023;13:656. [DOI] [PubMed] [PMC]

98. Leibold NS, Higgs NF, Kandler S, Khan A, Donato F, Andreae L. NMDA receptor activation drives early synapse formation in vivo. bioRxiv 595343 [Preprint]. 2024 [cited 2024 May 23]. Available from: https://doi.org/10.1101/2024.05.23.595343

99. Chittajallu R, Wester JC, Craig MT, Barksdale E, Yuan XQ, Akgül G, et al. Afferent specific role of NMDA receptors for the circuit integration of hippocampal neurogliaform cells. Nat Commun. 2017;8:152. [DOI] [PubMed] [PMC]

100. Park DK, Stein IS, Zito K. Ion flux-independent NMDA receptor signaling. Neuropharmacology. 2022; 210:109019. [DOI] [PubMed] [PMC]

101. Iacobucci GJ, Popescu GK. NMDA receptors: linking physiological output to biophysical operation. Nat Rev Neurosci. 2017;18:236–49. [DOI] [PubMed] [PMC]

102. Komuro H, Rakic P. Modulation of neuronal migration by NMDA receptors. Science. 1993;260:95–7. [DOI] [PubMed]

103. Napoli AJ, Laderwager S, Zoodsma JD, Biju B, Mucollari O, Schubel SK, et al. Developmental loss of NMDA receptors results in supernumerary forebrain neurons through delayed maturation of transit-amplifying neuroblasts. Sci Rep. 2024;14:3395. [DOI] [PubMed] [PMC]

104. Newton K. RIPK1 and RIPK3: critical regulators of inflammation and cell death. Trends Cell Biol. 2015;25:347–53. [DOI] [PubMed]

105. Clucas J, Meier P. Roles of RIPK1 as a stress sentinel coordinating cell survival and immunogenic cell death. Nat Rev Mol Cell Biol. 2023;24:835–52. [DOI] [PubMed]

106. Newton K. Multitasking Kinase RIPK1 Regulates Cell Death and Inflammation. Cold Spring Harb Perspect Biol. 2020;12:a036368. [DOI] [PubMed] [PMC]

107. Kondylis V, Kumari S, Vlantis K, Pasparakis M. The interplay of IKK, NF-κB and RIPK1 signaling in the regulation of cell death, tissue homeostasis and inflammation. Immunol Rev. 2017;277:113–27. [DOI] [PubMed]

108. Zhang T, Xu D, Trefts E, Lv M, Inuzuka H, Song G, et al. Metabolic orchestration of cell death by AMPK-mediated phosphorylation of RIPK1. Science. 2023;380:1372–80. [DOI] [PubMed] [PMC]

109. Wu W, Wang X, Berleth N, Deitersen J, Wallot-Hieke N, Böhler P, et al. The Autophagy-Initiating Kinase ULK1 Controls RIPK1-Mediated Cell Death. Cell Rep. 2020;31:107547. [DOI] [PubMed]

110. Fischer FA, Demarco B, Min FCH, Yeap HW, De Nardo D, Chen KW, et al. TBK1 and IKKε prevent premature cell death by limiting the activity of both RIPK1 and NLRP3 death pathways. Sci Adv. 2025;11:eadq1047. [DOI] [PubMed] [PMC]

111. Imai T, Lin J, Kaya GG, Ju E, Kondylis V, Kelepouras K, et al. The RIPK1 death domain restrains ZBP1- and TRIF-mediated cell death and inflammation. Immunity. 2024;57:1497–513. [DOI] [PubMed]

112. Massey CA, Thompson SJ, Ostrom RW, Drabek J, Sveinsson OA, Tomson T, et al. X-linked serotonin 2C receptor is associated with a non-canonical pathway for sudden unexpected death in epilepsy. Brain Commun. 2021;3:fcab149. [DOI] [PubMed] [PMC]

113. Klassen TL, Bomben VC, Patel A, Drabek J, Chen TT, Gu W, et al. High-resolution molecular genomic autopsy reveals complex sudden unexpected death in epilepsy risk profile. Epilepsia. 2014;55:e6–12. [DOI] [PubMed] [PMC]
114. Schoch GA, D'Arcy B, Stihle M, Burger D, Bär D, Benz J, et al. Molecular switch in the glucocorticoid receptor: active and passive antagonist conformations. J Mol Biol. 2010;395:568–77. [DOI] [PubMed]
115. Cubilla MA, Bermúdez V, Marquioni Ramella MD, Bachor TP, Suburo AM. Mifepristone, a blocker of glucocorticoid receptors, promotes photoreceptor death. Invest Ophthalmol Vis Sci. 2013;54:313–22. [DOI] [PubMed]
116. Oomen CA, Mayer JL, de Kloet ER, Joëls M, Lucassen PJ. Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the reduction in neurogenesis after chronic stress. Eur J Neurosci. 2007;26:3395–401. [DOI] [PubMed]
117. Ma P, Zhang Y, Liang Q, Yin Y, Wang S, Han R, et al. Mifepristone (RU486) inhibits dietary lipid digestion by antagonizing the role of glucocorticoid receptor on lipase transcription. iScience. 2021;24:102507. [DOI] [PubMed] [PMC]
118. Castinetti F, Conte-Devolx B, Brue T. Medical treatment of Cushing's syndrome: glucocorticoid receptor antagonists and mifepristone. Neuroendocrinology. 2010;92:125–30. [DOI] [PubMed]
119. Molitch ME. Glucocorticoid receptor blockers. Pituitary. 2022;25:733–6. [DOI] [PubMed]
120. Fleseriu M, Molitch ME, Gross C, Schteingart DE, Vaughan TB 3rd, Biller BMK. A new therapeutic approach in the medical treatment of Cushing's syndrome: glucocorticoid receptor blockade with mifepristone. Endocr Pract. 2013;19:313–26. [DOI] [PubMed]
121. Koenig HN, Olive MF. The glucocorticoid receptor antagonist mifepristone reduces ethanol intake in rats under limited access conditions. Psychoneuroendocrinology. 2004;29:999–1003. [DOI] [PubMed]
122. Newton R, Holden NS. Separating transrepression and transactivation: a distressing divorce for the glucocorticoid receptor? Mol Pharmacol. 2007;72:799–809. [DOI] [PubMed]
123. Oakley RH, Cruz-Topete D, He B, Foley JF, Myers PH, Xu X, et al. Cardiomyocyte glucocorticoid and mineralocorticoid receptors directly and antagonistically regulate heart disease in mice. Sci Signal. 2019;12:eaau9685. [DOI] [PubMed] [PMC]
124. Meduri GU, Chrousos GA. General Adaptation in Critical Illness: The Glucocorticoid Signaling System as Master Rheostat of Homeostatic Corrections in Concerted Action with Nuclear Factor-kB. In: Fink G, editor. Handbook of Stress: Stress, Immunology and Inflammation. Academic Press; 2024. pp. 231–61. [DOI]
125. Bose SK, Hutson I, Harris CA. Hepatic Glucocorticoid Receptor Plays a Greater Role Than Adipose GR in Metabolic Syndrome Despite Renal Compensation. Endocrinology. 2016;157:4943–60. [DOI] [PubMed] [PMC]
126. Watson ML, Baehr LM, Reichardt HM, Tuckermann JP, Bodine SC, Furlow JD. A cell-autonomous role for the glucocorticoid receptor in skeletal muscle atrophy induced by systemic glucocorticoid exposure. Am J Physiol Endocrinol Metab. 2012;302:E1210–20. [DOI] [PubMed] [PMC]
127. de Kloet ER, Meijer OC, de Nicola AF, de Rijk RH, Joëls M. Importance of the brain corticosteroid receptor balance in metaplasticity, cognitive performance and neuro-inflammation. Front Neuroendocrinol. 2018;49:124–45. [DOI] [PubMed]
128. Chantong B, Kratschmar DV, Nashev LG, Balazs Z, Odermatt A. Mineralocorticoid and glucocorticoid receptors differentially regulate NF-kappaB activity and pro-inflammatory cytokine production in murine BV-2 microglial cells. J Neuroinflammation. 2012;9:260. [DOI] [PubMed] [PMC]
129. Moran TJ, Gray S, Mikosz CA, Conzen SD. The glucocorticoid receptor mediates a survival signal in human mammary epithelial cells. Cancer Res. 2000;60:867–72. [PubMed]
130. Gao H, Li Y, Chen X. Interactions between nuclear receptors glucocorticoid receptor α and peroxisome proliferator-activated receptor α form a negative feedback loop. Rev Endocr Metab Disord. 2022;23:893–903. [DOI] [PubMed]

131. De Bosscher K, Desmet SJ, Clarisse D, Estébanez-Perpiña E, Brunsveld L. Nuclear receptor crosstalk - defining the mechanisms for therapeutic innovation. Nat Rev Endocrinol. 2020;16:363–77. [DOI] [PubMed]
132. Yang F, Ma Q, Liu Z, Li W, Tan Y, Jin C, et al. Glucocorticoid Receptor: MegaTrans Switching Mediates the Repression of an ERα-Regulated Transcriptional Program. Mol Cell. 2017;66:321–31. [DOI] [PubMed] [PMC]
133. Lee H, Gao X, Barrasa MI, Li H, Elmes RR, Peters LL, et al. PPAR-α and glucocorticoid receptor synergize to promote erythroid progenitor self-renewal. Nature. 2015;522:474–7. [DOI] [PubMed] [PMC]
134. Bougarne N, Mylka V, Ratman D, Beck IM, Thommis J, De Cauwer L, et al. Mechanisms Underlying the Functional Cooperation Between PPARα and GRα to Attenuate Inflammatory Responses. Front Immunol. 2019;10:1769. [DOI] [PubMed] [PMC]
135. Bougarne N, Paumelle R, Caron S, Hennuyer N, Mansouri R, Gervois P, et al. PPARalpha blocks glucocorticoid receptor alpha-mediated transactivation but cooperates with the activated glucocorticoid receptor alpha for transrepression on NF-kappaB. Proc Natl Acad Sci U S A. 2009;106: 7397–402. [DOI] [PubMed] [PMC]
136. Martinez G, Kipp Z, Stec D, Hinds T. Glucocorticoid Resistance Increases PPARγ Activity and Drives Hepatic Lipid Accumulation via Increased Eicosanoid and Monoacylglyceride Synthesis. Physiology. 2024;39:658. [DOI]
137. Standage SW, Bennion BG, Knowles TO, Ledee DR, Portman MA, McGuire JK, et al. PPARα augments heart function and cardiac fatty acid oxidation in early experimental polymicrobial sepsis. Am J Physiol Heart Circ Physiol. 2017;312:H239–49. [DOI] [PubMed] [PMC]
138. Ratman D, Mylka V, Bougarne N, Pawlak M, Caron S, Hennuyer N, et al. Chromatin recruitment of activated AMPK drives fasting response genes co-controlled by GR and PPARα. Nucleic Acids Res. 2016;44:10539–53. [DOI] [PubMed] [PMC]
139. Zhong J, Ji X, Zhao Y, Jia Y, Song C, Lv J, et al. Identification of BAF60b as a Chromatin-Remodeling Checkpoint of Diet-Induced Fatty Liver Disease. Diabetes. 2024;73:1615–30. [DOI] [PubMed] [PMC]
140. Witzel M, Petersheim D, Fan Y, Bahrami E, Racek T, Rohlfs M, et al. Chromatin-remodeling factor SMARCD2 regulates transcriptional networks controlling differentiation of neutrophil granulocytes. Nat Genet. 2017;49:742–52. [DOI] [PubMed] [PMC]
141. Morrison AJ. Chromatin-remodeling links metabolic signaling to gene expression. Mol Metab. 2020; 38:100973. [DOI] [PubMed] [PMC]
142. Tecle E, Warushavithana P, Li S, Blanchard MJ, Chhan CB, Bui T, et al. Conserved chromatin regulators control the transcriptional immune response to intracellular pathogens in Caenorhabditis elegans. PLoS Genet. 2025;21:e1011444. [DOI] [PubMed] [PMC]
143. Chinetti G, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. Inflamm Res. 2000;49: 497–505. [DOI] [PubMed]
144. Manoharan I, Suryawanshi A, Hong Y, Ranganathan P, Shanmugam A, Ahmad S, et al. Homeostatic PPARα Signaling Limits Inflammatory Responses to Commensal Microbiota in the Intestine. J Immunol. 2016;196:4739–49. [DOI] [PubMed] [PMC]
145. Koning ACAM, Buurstede JC, van Weert LTCM, Meijer OC. Glucocorticoid and Mineralocorticoid Receptors in the Brain: A Transcriptional Perspective. J Endocr Soc. 2019;3:1917–30. [DOI] [PubMed] [PMC]
146. Mifsud KR, Reul JMHM. Mineralocorticoid and glucocorticoid receptor-mediated control of genomic responses to stress in the brain. Stress. 2018;21:389–402. [DOI] [PubMed]
147. van der Heijden CDCC, Bode M, Riksen NP, Wenzel UO. The role of the mineralocorticoid receptor in immune cells in cardiovascular disease. Br J Pharmacol. 2022;179:3135–51. [DOI] [PubMed]

148. van der Heijden CDCC, Deinum J, Joosten LAB, Netea MG, Riksen NP. The mineralocorticoid receptor as a modulator of innate immunity and atherosclerosis. Cardiovasc Res. 2018;114:944–53. [DOI] [PubMed]
149. Gomez-Sanchez CE, de Rodriguez AF, Romero DG, Estess J, Warden MP, Gomez-Sanchez MT, et al. Development of a panel of monoclonal antibodies against the mineralocorticoid receptor. Endocrinology. 2006;147:1343–8. [DOI] [PubMed]
150. Nakamura T, Girerd S, Jaisser F, Barrera-Chimal J. Nonepithelial mineralocorticoid receptor activation as a determinant of kidney disease. Kidney Int Suppl (2011). 2022;12:12–8. [DOI] [PubMed] [PMC]
151. Bauersachs J, Lother A. Mineralocorticoid receptor activation and antagonism in cardiovascular disease: cellular and molecular mechanisms. Kidney Int Suppl (2011). 2022;12:19–26. [DOI] [PubMed] [PMC]
152. Bauersachs J, López-Andrés N. Mineralocorticoid receptor in cardiovascular diseases-Clinical trials and mechanistic insights. Br J Pharmacol. 2022;179:3119–34. [DOI] [PubMed]
153. Barrera-Chimal J, Bonnard B, Jaisser F. Roles of Mineralocorticoid Receptors in Cardiovascular and Cardiorenal Diseases. Annu Rev Physiol. 2022;84:585–610. [DOI] [PubMed]
154. Ferrario CM, Schiffrin EL. Role of mineralocorticoid receptor antagonists in cardiovascular disease. Circ Res. 2015;116:206–13. [DOI] [PubMed] [PMC]
155. Cannavo A, Bencivenga L, Liccardo D, Elia A, Marzano F, Gambino G, et al. Aldosterone and Mineralocorticoid Receptor System in Cardiovascular Physiology and Pathophysiology. Oxid Med Cell Longev. 2018;2018:1204598. [DOI] [PubMed] [PMC]
156. Sztechman D, Czarzasta K, Cudnoch-Jedrzejewska A, Szczepanska-Sadowska E, Zera T. Aldosterone and mineralocorticoid receptors in regulation of the cardiovascular system and pathological remodelling of the heart and arteries. J Physiol Pharmacol. 2018;69:829–45. [DOI] [PubMed]
157. Pandey AK, Bhatt DL, Cosentino F, Marx N, Rotstein O, Pitt B, et al. Non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease. Eur Heart J. 2022;43:2931–45. [DOI] [PubMed]
158. Feraco A, Marzolla V, Scuteri A, Armani A, Caprio M. Mineralocorticoid Receptors in Metabolic Syndrome: From Physiology to Disease. Trends Endocrinol Metab. 2020;31:205–17. [DOI] [PubMed]
159. Thuzar M, Abdul Halim M, Stowasser M. The mineralocorticoid system, cardiometabolic health and its interplay with adipose tissue. J Endocrinol. 2024;263:e240119. [DOI] [PubMed]
160. Gorini S, Kim SK, Infante M, Mammi C, La Vignera S, Fabbri A, et al. Role of Aldosterone and Mineralocorticoid Receptor in Cardiovascular Aging. Front Endocrinol (Lausanne). 2019;10:584. [DOI] [PubMed] [PMC]
161. Faught E, Vijayan MM. The mineralocorticoid receptor is essential for stress axis regulation in zebrafish larvae. Sci Rep. 2018;8:18081. [DOI] [PubMed] [PMC]
162. Paul B, Sterner ZR, Bhawal R, Anderson ET, Zhang S, Buchholz DR. Impaired negative feedback and death following acute stress in glucocorticoid receptor knockout Xenopus tropicalis tadpoles. Gen Comp Endocrinol. 2022;326:114072. [DOI] [PubMed]
163. de Kloet ER, Joëls M. The cortisol switch between vulnerability and resilience. Mol Psychiatry. 2024;29:20–34. [DOI] [PubMed]
164. de Kloet ER, Otte C, Kumsta R, Kok L, Hillegers MHJ, Hasselmann H, et al. Stress and Depression: a Crucial Role of the Mineralocorticoid Receptor. J Neuroendocrinol. 2016;28:12379. [DOI] [PubMed]
165. Almeida OF, Condé GL, Crochemore C, Demeneix BA, Fischer D, Hassan AH, et al. Subtle shifts in the ratio between pro- and antiapoptotic molecules after activation of corticosteroid receptors decide neuronal fate. FASEB J. 2000;14:779–90. [DOI] [PubMed]
166. Sousa N, Cerqueira JJ, Almeida OFX. Corticosteroid receptors and neuroplasticity. Brain Res Rev. 2008;57:561–70. [DOI] [PubMed]
167. Le Menuet D, Lombès M. The neuronal mineralocorticoid receptor: from cell survival to neurogenesis. Steroids. 2014;91:11–9. [DOI] [PubMed]

168. Garcia A, Steiner B, Kronenberg G, Bick-Sander A, Kempermann G. Age-dependent expression of glucocorticoid- and mineralocorticoid receptors on neural precursor cell populations in the adult murine hippocampus. Aging Cell. 2004;3:363–71. [DOI] [PubMed]
169. Oakley RH, Whirledge SD, Petrillo MG, Riddick NV, Xu X, Moy SS, et al. Combinatorial actions of glucocorticoid and mineralocorticoid stress hormone receptors are required for preventing neurodegeneration of the mouse hippocampus. Neurobiol Stress. 2021;15:100369. [DOI] [PubMed] [PMC]
170. De Kloet ER, Vreugdenhil E, Oitzl MS, Joëls M. Brain corticosteroid receptor balance in health and disease. Endocr Rev. 1998;19:269–301. [DOI] [PubMed]
171. Derijk RH, de Kloet ER. Corticosteroid receptor polymorphisms: determinants of vulnerability and resilience. Eur J Pharmacol. 2008;583:303–11. [DOI] [PubMed]
172. Anderson SR, Roberts JM, Ghena N, Irvin EA, Schwakopf J, Cooperstein IB, et al. Neuronal apoptosis drives remodeling states of microglia and shifts in survival pathway dependence. Elife. 2022;11: e76564. [DOI] [PubMed] [PMC]
173. Spiess KL, Geden MJ, Romero SE, Hollville E, Hammond ES, Patterson RL, et al. Apoptosis signaling is activated as a transient pulse in neurons. Cell Death Differ. 2025;32:521–9. [DOI] [PubMed]
174. Sarubin N, Hilbert S, Naumann F, Zill P, Wimmer AM, Nothdurfter C, et al. The sex-dependent role of the glucocorticoid receptor in depression: variations in the NR3C1 gene are associated with major depressive disorder in women but not in men. Eur Arch Psychiatry Clin Neurosci. 2017;267:123–33. [DOI] [PubMed]
175. Palma-Gudiel H, Córdova-Palomera A, Leza JC, Fañanás L. Glucocorticoid receptor gene (NR3C1) methylation processes as mediators of early adversity in stress-related disorders causality: A critical review. Neurosci Biobehav Rev. 2015;55:520–35. [DOI] [PubMed]
176. Kumsta R, Kliegel D, Linden M, DeRijk R, de Kloet ER. Genetic variation of the mineralocorticoid receptor gene (MR, NR3C2) is associated with a conceptual endophenotype of “CRF-hypoactivity”. Psychoneuroendocrinology. 2019;105:79–85. [DOI] [PubMed]
177. Schmid W, Cole TJ, Blendy JA, Schütz G. Molecular genetic analysis of glucocorticoid signalling in development. J Steroid Biochem Mol Biol. 1995;53:33–5. [DOI] [PubMed]
178. Goldfeld AE, Firestone GL, Shaw PA, Gluecksohn-Waelsch S. Recessive lethal deletion on mouse chromosome 7 affects glucocorticoid receptor binding activities. Proc Natl Acad Sci U S A. 1983;80: 1431–4. [DOI] [PubMed] [PMC]
179. Berger S, Bleich M, Schmid W, Cole TJ, Peters J, Watanabe H, et al. Mineralocorticoid receptor knockout mice: pathophysiology of Na^+ metabolism. Proc Natl Acad Sci U S A. 1998;95:9424–9. [DOI] [PubMed] [PMC]
180. Berger S, Bleich M, Schmid W, Greger R, Schütz G. Mineralocorticoid receptor knockout mice: lessons on Na^+ metabolism. Kidney Int. 2000;57:1295–8. [DOI] [PubMed]
181. Cole TJ, Young MJ. 30 YEARS OF THE MINERALOCORTICOID RECEPTOR: Mineralocorticoid receptor null mice: informing cell-type-specific roles. J Endocrinol. 2017;234:T83–92. [DOI] [PubMed]
182. Joëls M, Karst H, DeRijk R, de Kloet ER. The coming out of the brain mineralocorticoid receptor. Trends Neurosci. 2008;31:1–7. [DOI] [PubMed]
183. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med. 2005;353:1711–23. [DOI] [PubMed]
184. Usher MG, Duan SZ, Ivaschenko CY, Frieler RA, Berger S, Schütz G, et al. Myeloid mineralocorticoid receptor controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice. J Clin Invest. 2010;120:3350–64. [DOI] [PubMed] [PMC]
185. Ehrchen J, Steinmüller L, Barczyk K, Tenbrock K, Nacken W, Eisenacher M, et al. Glucocorticoids induce differentiation of a specifically activated, anti-inflammatory subtype of human monocytes. Blood. 2007;109:1265–74. [DOI] [PubMed]

186. Sun Y, Zhang J, Lu L, Chen SS, Quinn MT, Weber KT. Aldosterone-induced inflammation in the rat heart: role of oxidative stress. Am J Pathol. 2002;161:1773–81. [DOI] [PubMed] [PMC]
187. Rocha R, Rudolph AE, Frierdich GE, Nachowiak DA, Kekec BK, Blomme EAG, et al. Aldosterone induces a vascular inflammatory phenotype in the rat heart. Am J Physiol Heart Circ Physiol. 2002; 283:H1802–10. [DOI] [PubMed]
188. Shibata S, Nagase M, Yoshida S, Kawarazaki W, Kurihara H, Tanaka H, et al. Modification of mineralocorticoid receptor function by Rac1 GTPase: implication in proteinuric kidney disease. Nat Med. 2008;14:1370–6. [DOI] [PubMed]
189. Rickard AJ, Morgan J, Tesch G, Funder JW, Fuller PJ, Young MJ. Deletion of mineralocorticoid receptors from macrophages protects against deoxycorticosterone/salt-induced cardiac fibrosis and increased blood pressure. Hypertension. 2009;54:537–43. [DOI] [PubMed]
190. Tonsing-Carter E, Hernandez KM, Kim CR, Harkless RV, Oh A, Bowie KR, et al. Glucocorticoid receptor modulation decreases ER-positive breast cancer cell proliferation and suppresses wild-type and mutant ER chromatin association. Breast Cancer Res. 2019;21:82. [DOI] [PubMed] [PMC]
191. Liu Y, Brent GA. Thyroid hormone crosstalk with nuclear receptor signaling in metabolic regulation. Trends Endocrinol Metab. 2010;21:166–73. [DOI] [PubMed] [PMC]
192. Bagamasbad P, Denver RJ. Mechanisms and significance of nuclear receptor auto- and cross-regulation. Gen Comp Endocrinol. 2011;170:3–17. [DOI] [PubMed] [PMC]
193. Wang L, Zhang X, Farrar WL, Yang X. Transcriptional crosstalk between nuclear receptors and cytokine signal transduction pathways in immunity. Cell Mol Immunol. 2004;1:416–24. [PubMed]
194. Pascussi JM, Gerbal-Chaloin S, Duret C, Daujat-Chavanieu M, Vilarem MJ, Maurel P. The tangle of nuclear receptors that controls xenobiotic metabolism and transport: crosstalk and consequences. Annu Rev Pharmacol Toxicol. 2008;48:1–32. [DOI] [PubMed]
195. Ogawa S, Lozach J, Benner C, Pascual G, Tangirala RK, Westin S, et al. Molecular determinants of crosstalk between nuclear receptors and toll-like receptors. Cell. 2005;122:707–21. [DOI] [PubMed] [PMC]
196. Noh K, Chow ECY, Quach HP, Groothuis GMM, Tirona RG, Pang KS. Significance of the Vitamin D Receptor on Crosstalk with Nuclear Receptors and Regulation of Enzymes and Transporters. AAPS J. 2022;24:71. [DOI] [PubMed]
197. Meduri GU, Psarra AM, Amrein K. General Adaptation in Critical Illness 2: The Glucocorticoid Signaling System as a Master Rheostat of Homeostatic Corrections in Concerted Action with Mitochondrial and Essential Micronutrient Support. In: Fink G, editor. Handbook of Stress: Stress, Immunology and Inflammation. Academic Press; 2024. pp. 263–87. [DOI]
198. Meduri GU, Annane D, Chrousos GP, Marik PE, Sinclair SE. Activation and regulation of systemic inflammation in ARDS: rationale for prolonged glucocorticoid therapy. Chest. 2009;136:1631–43. [DOI] [PubMed]
199. Natsaridis E, Perdikaris P, Fokos S, Dermon CR. Neuronal and Astroglial Localization of Glucocorticoid Receptor GRα in Adult Zebrafish Brain (*Danio rerio*). Brain Sci. 2023;13:861. [DOI] [PubMed] [PMC]
200. Jiang C, Liu L, Tasker JG. Why do we need nongenomic glucocorticoid mechanisms? Front Neuroendocrinol. 2014;35:72–5. [DOI] [PubMed]
201. Panettieri RA, Schaafsma D, Amrani Y, Koziol-White C, Ostrom R, Tliba O. Non-genomic Effects of Glucocorticoids: An Updated View. Trends Pharmacol Sci. 2019;40:38–49. [DOI] [PubMed] [PMC]
202. Mom R, Réty S, Auguin D. Cortisol Interaction with Aquaporin-2 Modulates Its Water Permeability: Perspectives for Non-Genomic Effects of Corticosteroids. Int J Mol Sci. 2023;24:1499. [DOI] [PubMed] [PMC]
203. Groeneweg FL, Karst H, de Kloet ER, Joëls M. Rapid non-genomic effects of corticosteroids and their role in the central stress response. J Endocrinol. 2011;209:153–67. [DOI] [PubMed]
204. Joëls M. Corticosteroids and the brain. J Endocrinol. 2018;238:R121–30. [DOI] [PubMed]

205. Karst H, den Boon FS, Vervoort N, Adrian M, Kapitein LC, Joëls M. Non-genomic steroid signaling through the mineralocorticoid receptor: Involvement of a membrane-associated receptor? Mol Cell Endocrinol. 2022;541:111501. [DOI] [PubMed]

206. Meduri GU. Glucocorticoids and GRα Signaling in Critical Illness: Phase-Specific Homeostatic Corrections Across Systems. Semin Respir Crit Care Med. 2025;[Epub ahead of print]. [DOI] [PubMed]