Integrative neurogenomic and physiological perspectives on stress response in European rabbit (*Oryctolagus cuniculus*): from HPA axis regulation to the gut–brain axis

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Abstract. This mini-review synthesizes current knowledge on the biological mechanisms underlying stress responses in European rabbit (*Oryctolagus cuniculus*), with a particular emphasis on neuroendocrine regulation, transcriptomic dynamics, and systemic physiological integration. The hypothalamic–pituitary–adrenal (HPA) axis is examined as a central mediator of stress, highlighting the role of glucocorticoid signaling in modulating gene expression, neural plasticity, and behavioral outcomes. Recent advances in transcriptomics and epigenetics reveal that stress-induced molecular changes are highly cell-type-specific and may exhibit temporal persistence through chromatin remodeling and transcriptional memory. Beyond central mechanisms, the review explores the emerging significance of the gut–brain axis, emphasizing how microbiome-derived metabolites interact with neuroendocrine pathways to influence stress resilience and behavior. Environmental factors, including housing conditions, nutrition, and social interactions, are discussed as key modulators of both physiological stress responses and microbial composition. The integration of multi-omics approaches, encompassing transcriptomics, metabolomics, and microbiome profiling, is proposed as a powerful framework for identifying robust biomarkers of stress and welfare. Overall, this review advocates for a systems biology perspective, in which stress is understood as an emergent property of interconnected biological networks, with direct implications for improving rabbit welfare in both experimental and production settings.
Keywords: stress response, HPA axis, glucocorticoids, transcriptomics, epigenetics, gut–brain axis, microbiome, multi-omics, animal welfare, rabbits.

Introduction. Stress in European rabbit (*Oryctolagus cuniculus*) engages conserved neuroendocrine pathways and produces behavioral changes that are highly sensitive to housing and management (Bud et al., 2011; Petrescu-Mag et al., 2019). At the same time, work in other species shows that stress reshapes brain and hypothalamic–pituitary–adrenal (HPA)-axis transcriptomes, providing a mechanistic bridge between endocrine physiology, behavior and long-term welfare.

The aim of this mini-review is to provide an integrative overview of the mechanisms underlying stress responses in rabbits, bridging neuroendocrine regulation with molecular and systemic perspectives. Specifically, the study seeks to: (i) elucidate the role of the HPA axis

and glucocorticoid signaling in mediating stress-induced physiological and behavioral changes; (ii) examine the contribution of transcriptomic and epigenetic processes to stress adaptation and memory; (iii) highlight the importance of peripheral systems, particularly the gut–brain axis, in modulating neurobiological responses; and (iv) emphasize the value of multi-omics approaches for advancing the assessment of stress and animal welfare.

HPA Axis Dynamics and Behavioral Stress Phenotypes. The HPA axis is activated by corticotropin-releasing factor from the paraventricular nucleus (PVN), driving glucocorticoid secretion that orchestrates adaptive metabolic and behavioral responses to stress (Smith & Vale, 2006; Cabezas et al., 2007). Feedback via glucocorticoid receptors (GR) in the PVN and upstream limbic structures constrains response magnitude and duration; chronic activation can lead to hypersecretion, sensitized responses, or even adrenal exhaustion depending on stressor chronicity and modality (Cabezas et al., 2007; Herman et al., 2016; Knezevic et al., 2023). Cross-talk with the hypothalamic-pituitary-gonadal axis and sex steroids modulates HPA gain and aggression, with glucocorticoids and androgens jointly shaping stress-related behaviors (Verga et al., 2007; Girgenti et al., 2020). In rabbits, both acute and chronic stressors elevate circulating cortisol or corticosterone and their fecal metabolites, linking HPA activation to altered metabolism, maternal behavior and threat-sensitive survival strategies (Oyola & Handa, 2017; Benedek et al., 2021; Lopez et al., 2021; El-Sabrout et al., 2024) (Table 1).

Table 1

HPA-related outcomes in rabbits under stressful contexts: links between HPA activation, behavior and outcomes in rabbits

Context / Stressor	*Endocrine change / outcome*	*Behavioral or fitness link*	*References*
Captivity (2–4 weeks)	Moderately elevated corticosterone and fecal metabolites	Lower body condition but higher post-release survival	Benedek et al., 2021
Moderate vs. chronic experimental stress	Increased plasma cortisol and glucose; altered albumin, cholesterol	Indicates disrupted homeostasis, welfare concerns	Oyola & Handa, 2017
Predator pressure in the wild	Fecal corticosterone correlates positively with predator indices	Supports threat-sensitive stress physiology	Lopez et al., 2021
Periparturient stress in does	Higher cortisol metabolites around parturition	Delayed nest building, smaller litters, higher mortality	El-Sabrout et al., 2024

Transcriptomic Modifications in Stress-Responsive Circuits. Genome-wide transcriptomic studies in rodents and humans show that stress consistently reconfigures brain gene expression. Meta-analyses of stress-exposed brain transcriptomes identify recurrently regulated genes across species, sexes, and paradigms, as well as overlap between animal models and post-traumatic stress disorder (PTSD) patients (Monclús et al., 2008; Mbiydzenyuy & Qulu, 2024). Chronic stress in the prefrontal cortex produces a robust signature with downregulation of glial/myelin and vascular pathways and suppression of immediate-early genes such as Fos, Junb, Arc and Dusp1, linking molecular changes to altered plasticity and psychiatric-like phenotypes (Monclús et al., 2008; Xiong et al., 2026). Single-cell profiling across all three HPA components reveals stress-sensitive cell types and identifies adrenal ABCB1 as a key regulator of glucocorticoid handling and stress adaptation (Ozella et al., 2024). More broadly, single-cell and spatial transcriptomics now resolve subtle cell-state shifts in CNS stress circuits, providing tools readily transferable to rabbit neurogenomics (Hansen & Berthelsen, 2000). These findings imply that in rabbits, chronic activation of the HPA axis by housing, social or thermal stressors is likely to be accompanied

by cell-type-specific transcriptional remodeling in hypothalamus, pituitary, adrenal and limbic regions, although direct rabbit brain transcriptomes under stress remain to be generated.

Epigenomic Regulation and Long-Term Programming of Stress Responses in Rabbit. Beyond transient transcriptional responses, stress exerts durable effects on neural function through epigenomic remodeling that stabilizes or constrains gene expression states across time (Trollope et al., 2011; Weaver et al., 2017; Villagómez-Aranda et al., 2022; Nicolaides et al., 2023). In mammals, glucocorticoid signaling interacts directly with chromatin architecture via ligand-activated GR, which bind to glucocorticoid response elements and recruit chromatin-modifying complexes (Trollope et al., 2011; Kim et al., 2012; Stenz et al., 2018). This process induces coordinated changes in DNA methylation, histone post-translational modifications, and chromatin accessibility, thereby encoding prior stress exposure into a persistent molecular memory (Horowitz, 2016; Weaver et al., 2017; Claydon & Conway-Campbell, 2022; Daskalakis et al., 2022; Nicolaides et al., 2023). Although such mechanisms remain largely unexplored in rabbits, their conservation across vertebrates strongly suggests similar regulatory dynamics in lagomorph stress neurobiology (Weaver et al., 2017; Cruceanu et al., 2021; Claydon & Conway-Campbell, 2022; De Donno et al., 2026).

One key feature of stress-induced epigenomic regulation is its cell-type specificity. In limbic and hypothalamic circuits, neuronal and glial populations exhibit distinct chromatin responses to glucocorticoids, reflecting differences in receptor density, cofactor availability, and basal transcriptional states (Kim et al., 2012; Vukojević et al., 2014; Jiang et al., 2019; Viho et al., 2021). Chronic stress is associated with increased DNA methylation at promoters of plasticity-related genes and concomitant reductions in their expression, while enhancers linked to inflammatory and metabolic pathways often become more accessible (Tammen et al., 2013; Weaver et al., 2017; Bartlett et al., 2019; Coley et al., 2019; Claydon & Conway-Campbell, 2022;). This bidirectional remodeling provides a mechanistic substrate for the coexistence of impaired synaptic plasticity and heightened neuroimmune signaling observed under prolonged stress conditions (Weaver et al., 2017; Abellán-Álvaro et al., 2021; Cruceanu et al., 2021; Claydon & Conway-Campbell, 2022).

Importantly, epigenomic modifications introduce a temporal dimension that bridges acute stress exposure and long-term behavioral phenotypes (Horowitz, 2016; Weaver et al., 2017; Claydon & Conway-Campbell, 2022; De Donno et al., 2026). In rabbits, where early-life conditions such as maternal care, periparturient stress, and environmental predictability vary substantially across production and laboratory systems, such mechanisms are likely to contribute to developmental programming of stress reactivity (Weaver et al., 2017; Bartlett et al., 2019; Cruceanu et al., 2021; Claydon & Conway-Campbell, 2022). Altered epigenetic states in hypothalamic or limbic regions could recalibrate HPA axis sensitivity, influencing baseline glucocorticoid levels, feedback efficiency, and behavioral coping strategies later in life (Weaver et al., 2017; Bartlett et al., 2019; Abellán-Álvaro et al., 2021; Claydon & Conway-Campbell, 2022). This is particularly relevant given evidence from other mammals that early environmental perturbations can produce stable inter-individual differences in anxiety-like behavior, social interaction, and cognitive flexibility (Weaver et al., 2017; Bartlett et al., 2019; Abellán-Álvaro et al., 2021; Cruceanu et al., 2021; Claydon & Conway-Campbell, 2022;).

Another critical aspect is the potential reversibility of epigenomic marks (Horowitz, 2016; Weaver et al., 2017; Stenz et al., 2018; Bothe et al., 2021; Daskalakis et al., 2022; De Donno et al., 2026). Environmental enrichment, social stability, and reduced chronic stress exposure have been shown in other species to partially restore chromatin accessibility and normalize gene expression profiles (Horowitz, 2016; Weaver et al., 2017; Stenz et al., 2018; Bothe et al., 2021; Leung et al., 2022). In rabbits, this raises the possibility that welfare-improving interventions do not merely affect behavior and endocrine outputs acutely but may also reprogram underlying regulatory landscapes (Horowitz, 2016; Weaver et al., 2017; Bothe et al., 2021; Daskalakis et al., 2022; De Donno et al., 2026). Consequently, epigenomic profiling, through assays such as ATAC-seq, ChIP-seq, and DNA methylation mapping,

represents a promising yet underutilized approach for identifying biomarkers of chronic stress and recovery in this species (Tammen et al., 2013; Horowitz, 2016; Stenz et al., 2018; Coley et al., 2019; Leung et al., 2022).

Integrating epigenomic data with transcriptomic and endocrine measures would therefore provide a more complete understanding of stress biology in rabbits (Tammen et al., 2013; Weaver et al., 2017; Coley et al., 2019; Claydon & Conway-Campbell, 2022; De Donno et al., 2026). Such an approach could reveal whether observed behavioral phenotypes arise from transient transcriptional fluctuations or from stabilized regulatory states that predispose individuals to resilience or vulnerability (Weaver et al., 2017; Bartlett et al., 2019; Abellán-Álvaro et al., 2021; Cruceanu et al., 2021; Claydon & Conway-Campbell, 2022). This distinction is critical for both experimental interpretation and the design of housing and management systems aimed at promoting long-term welfare (Horowitz, 2016; Weaver et al., 2017; Cruceanu et al., 2021; Claydon & Conway-Campbell, 2022; De Donno et al., 2026).

Behavioral Changes, Welfare, and Their Endocrine–Genomic Interface. Rabbit welfare research documents clear links between environment, behavior and physiological stress markers. Group-housed rabbits display richer locomotor and exploratory repertoires but also elevated salivary and hair corticosterone, indicating that social opportunities can coexist with high acute and chronic stress if aggression and dominance are not controlled (Lazăr et al., 2024). Single-cage housing shows reduced kinetic and social behavior and increased indicators of acute stress such as stereotypic turning (Lazăr et al., 2024). Conventional barren cages increase restlessness, excessive grooming, bar-gnawing and timidity compared with enriched cages that offer shelter and vertical complexity, suggesting elevated psychological stress in standard systems (Stankiewicz et al., 2022). Environmental enrichment (toys, destructible objects, dig bins, elevated space) promotes active, species-typical behaviors in laboratory rabbits and is interpreted as improved welfare, even when fecal glucocorticoids are unchanged (Coda et al., 2020; James et al., 2023; Piwecka et al., 2023). Reviews of farm and lab rabbits identify social stress, fear, heat and restrictive housing as major psychological and physical stressors, and emphasize neuroendocrine (HPA, neuroimmune) and behavioral indicators as core welfare metrics (Coda et al., 2020; James et al., 2023; Piwecka et al., 2023). Given the strong evidence from other mammals that HPA-driven glucocorticoid signaling exerts powerful transcriptional control over genes involved in synaptic plasticity, neuroimmune function and vascular biology (Smith & Vale, 2006; Cabezas et al., 2007; Monclús et al., 2008; Herman et al., 2016; Ozella et al., 2024; Xiong et al., 2026), these housing and management-related stressors in rabbits likely engage conserved molecular programs in brain and adrenal tissues that shape long-term behavior, resilience and vulnerability.

Peripheral–Central Integration: Neuroimmune, Metabolic, and Microbiome Contributions to Stress Phenotypes. Peripheral–Central Integration: Neuroimmune, Metabolic, and Microbiome Contributions to Stress Phenotypes. Stress responses are not confined to the central nervous system but emerge from dynamic interactions between brain circuits and peripheral physiological systems (Russell & Lightman, 2019; Shimba & Ikuta, 2020). In rabbits, as in other mammals, the integration of neuroendocrine, immune, metabolic, and microbial signals forms a distributed network that shapes behavioral outputs and long-term adaptation (van de Wouw et al., 2018; Kivimäki et al., 2022; Townsend & Steinberg, 2023). This systems-level perspective extends beyond the classical HPA axis framework and is essential for understanding variability in stress susceptibility under different environmental conditions (Russell & Lightman, 2019; Shimba & Ikuta, 2020; Beale et al., 2025). A central component of this integration is the neuroimmune interface. Glucocorticoids modulate immune cell function, cytokine production, and inflammatory signaling, while peripheral immune mediators can in turn influence brain activity through humoral pathways, neural afferents, and blood–brain barrier interactions (O'Riordan et al., 2022; Fabrile et al.,

2023; Burke et al., 2024; Choudhary et al., 2024). Chronic stress is often associated with a low-grade pro-inflammatory state, which can alter synaptic function, neurotransmitter systems, and neural plasticity . In rabbits exposed to persistent social or environmental stressors, such bidirectional signaling may contribute to behavioral alterations such as heightened vigilance, reduced exploratory behavior, or increased aggression (Fabrile et al., 2023; Hassamal, 2023; Choudhary et al., 2024). Although direct neuroimmune transcriptomic data in rabbits are scarce, the conservation of these pathways suggests that similar mechanisms underlie observed welfare-related phenotypes (van de Wouw et al., 2018; Kivimäki et al., 2022; Hassamal, 2023; Burke et al., 2024).

Metabolic regulation represents another critical axis of integration. Glucocorticoid-driven changes in glucose homeostasis, lipid metabolism, and protein turnover provide the energetic substrate for stress responses but can become maladaptive under chronic activation (Russell & Lightman, 2019; Shimba & Ikuta, 2020; Seal & Turner, 2021; Kumar et al., 2022). In rabbits, shifts in metabolic state, reflected in altered glucose, cholesterol, and albumin levels, are already linked to stress exposure (van de Wouw et al., 2018; Shimba & Ikuta, 2020; Kumar et al., 2022). These metabolic changes can feedback to the brain via hormonal signals such as insulin and leptin, influencing hypothalamic circuits that regulate both energy balance and stress responsiveness (Shimba & Ikuta, 2020; Silva et al., 2020; Kumar et al., 2022). Consequently, metabolic status may modulate not only physiological resilience but also behavioral strategies, including risk assessment and foraging-related activity (Shimba & Ikuta, 2020; Seal & Turner, 2021; Kumar et al., 2022). An emerging and particularly relevant dimension is the role of the gut–brain axis. Rabbits possess a highly specialized digestive system with extensive hindgut fermentation, making them especially sensitive to alterations in gut microbiota composition. Stress-induced changes in microbial communities can affect the production of neuroactive metabolites, short-chain fatty acids, and immune-modulating compounds. These signals can reach the central nervous system via vagal pathways, systemic circulation, or immune mediators, thereby influencing neural function and behavior (Suravajhala et al., 2016; Rabasa & Dickson, 2016; Guo et al., 2022; Meyer et al., 2023; Beale et al., 2025; Xu et al., 2025). Conversely, housing conditions, diet, and social interactions, key determinants of welfare—also shape the microbiome, creating a complex feedback loop between environment, physiology, and behavior (van de Wouw et al., 2018; Cryan et al., 2019; Kivimäki et al., 2022; Hassamal, 2023; Meyer et al., 2023; Beale et al., 2025).

This integrative framework has important implications for rabbit welfare science and neurogenomics. It suggests that transcriptomic changes observed in brain or adrenal tissues cannot be fully interpreted in isolation but must be contextualized within organism-wide physiological states. Multi-omics approaches that combine central and peripheral data, such as brain transcriptomics, circulating metabolomics, immune profiling, and microbiome sequencing, would enable a more comprehensive characterization of stress phenotypes. Such strategies could identify convergent biomarkers that reflect the cumulative impact of environmental stressors and provide more sensitive indicators of welfare than single-parameter measures (van de Wouw et al., 2018; Cryan et al., 2019; Kivimäki et al., 2022; Meyer et al., 2023; Townsend & Steinberg, 2023).

Ultimately, viewing stress in rabbits as an emergent property of interconnected biological systems shifts the focus from isolated pathways to network dynamics as summarized in Figure 1. This perspective not only aligns with contemporary systems biology but also offers a more robust foundation for designing interventions that improve resilience, reduce chronic stress burden, and promote adaptive behavioral repertoires in both laboratory and production settings (van de Wouw et al., 2018; Cryan et al., 2019; Kivimäki et al., 2022; Townsend & Steinberg, 2023; Beale et al., 2025).

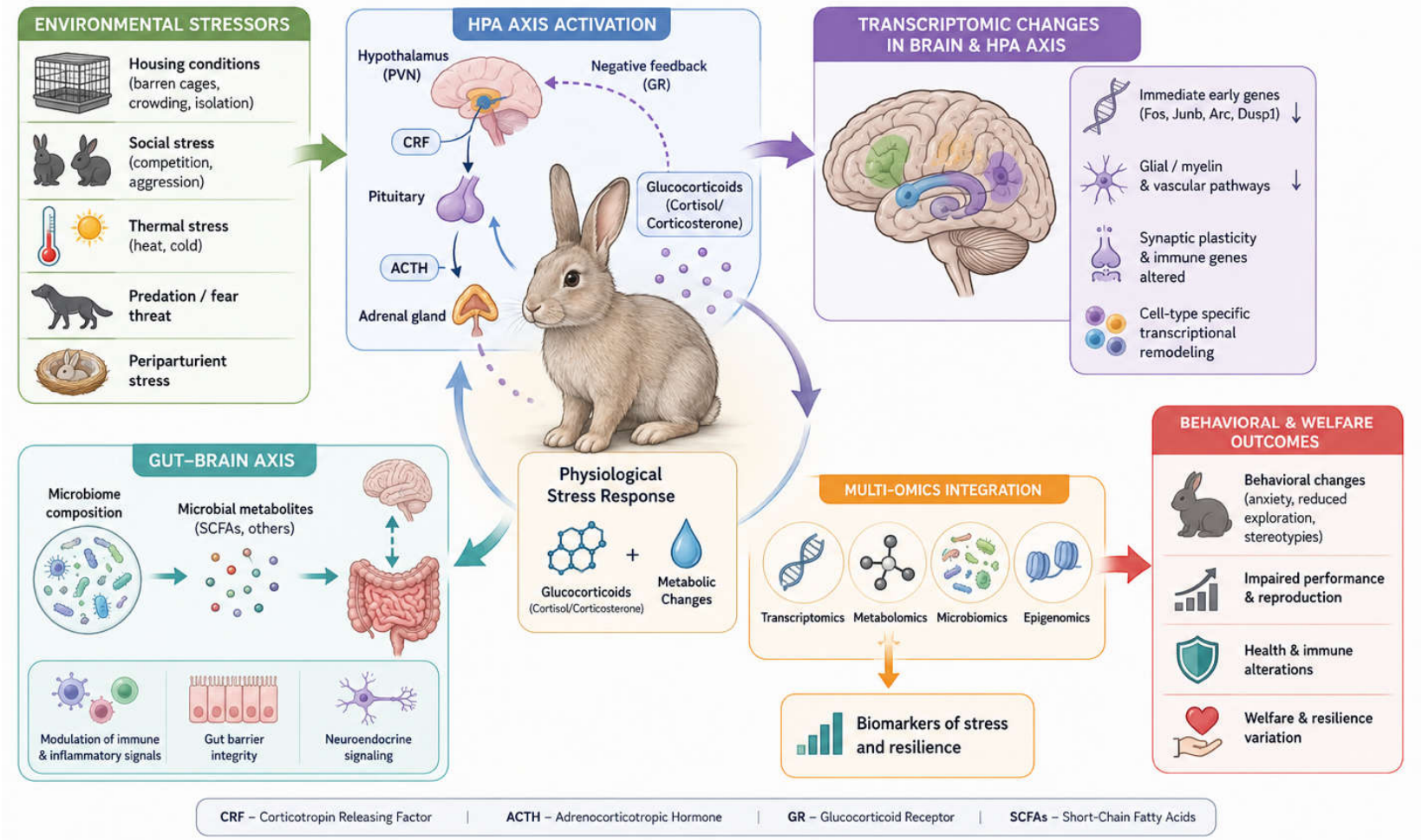

Figure 1. Neurogenomics of stress and behavior in rabbits: from environment to molecular and behavioral outcomes. This diagram summarizes the interactions between environmental stressors, hypothalamic-pituitary-adrenal (HPA) axis activation, glucocorticoid signaling, transcriptomic and epigenetic regulation, and peripheral systems including immune, metabolic, and gut–brain axis pathways, illustrating how these mechanisms collectively shape behavioral and welfare outcomes. The figure effectively represents the mechanistic conclusion of the Peripheral-Central Integration section, bridging the detailed discussion of central and peripheral stress responses to the overall conclusions of the review.

Conclusions. Stress in rabbits should be conceptualized as a multidimensional and system-level phenomenon involving dynamic interactions between neuroendocrine, molecular, metabolic, and microbial components. While the HPA axis remains a central regulatory framework, accumulating evidence demonstrates that transcriptomic plasticity, epigenetic modulation, and microbiome-derived signaling significantly contribute to the complexity of stress responses. The gut–brain axis, in particular, represents a critical interface linking environmental conditions to neural and behavioral outcomes. Importantly, single-layer analyses are insufficient to capture this complexity, underscoring the necessity of integrative, multi-omics strategies. Such approaches hold promise for identifying sensitive and reliable biomarkers of stress, thereby improving both experimental interpretation and practical welfare assessment. Ultimately, adopting a systems biology perspective will enhance our capacity to design targeted interventions that promote resilience, reduce chronic stress, and optimize welfare in rabbit populations.

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