Literature Review: Neuropeptide Y, the Hypothalamic–Pituitary–Adrenal Axis, and Autonomic Regulation

Author Name

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Abstract

Neuropeptide Y (NPY) and the hypothalamic–pituitary–adrenal (HPA) axis sit at a key junction between endocrine stress signaling and autonomic regulation. NPY acts as a sympathetic cotransmitter in the periphery, where it amplifies vasoconstriction and vascular reactivity, but it also has central, circuit-specific effects within hypothalamic stress networks. The literature shows that NPY can both facilitate HPA output near corticotropin-releasing hormone (CRH) neurons and suppress sympathetic outflow through Y_1-dependent hypothalamic circuits, implying that receptor subtype, anatomical location, and timescale matter. Human work most strongly links low NPY signaling to impaired stress resilience, especially in post-traumatic stress disorder (PTSD), where reduced cerebrospinal fluid NPY coexists with evidence of central HPA-axis dysregulation and autonomic hyperarousal. The current therapeutic frontier therefore has three layers: direct but still early-phase NPY replacement strategies, mature HPA-axis-targeted treatments for hypercortisolism, and autonomic neuromodulation approaches such as vagus nerve stimulation that aim to rebalance the same integrated stress network.

1 Scope and terminology

This review treats the user's phrase "hypothalamic-pituitary axis" as the hypothalamic–pituitary–adrenal (HPA) axis, because that is the endocrine stress axis most directly coupled to autonomic regulation. The central question is how NPY and HPA signaling jointly shape sympathetic and parasympathetic output, and which interventions are currently most clinically relevant.

At a systems level, the autonomic nervous system (ANS) and HPA axis are complementary outputs of the brain's stress network rather than isolated pathways. The ANS produces the fast phase of the stress response through sympathetic activation and vagal withdrawal, whereas the HPA axis produces a slower endocrine response through CRH, adrenocorticotropic hormone (ACTH), and glucocorticoids. NPY intersects both limbs: it is a peripheral sympathetic cotransmitter and a central hypothalamic and limbic neuromodulator. For that reason, it is especially useful when reviewing disorders marked by hyperarousal, cardiometabolic strain, trauma reactivity, or overt hypercortisolism.

2 Mechanistic overview: why NPY matters

NPY is a 36-amino-acid peptide expressed in both central and peripheral nervous systems. In the periphery, it is co-released with norepinephrine and ATP from sympathetic nerves, and human vascular studies show that it both directly constricts small arteries and amplifies other sympathetic vasoconstrictor signals.[1, 2] This makes NPY relevant to blood pressure control, vascular tone, and the cardiovascular load of chronic stress.

Within the hypothalamus, NPY fibers from the arcuate nucleus project to the paraventricular nucleus (PVN), where they make close appositions onto CRH neurons.[3, 4] Early PVN microinjection studies showed that local NPY can increase ACTH and corticosterone release, indicating that NPY can activate the HPA axis when delivered to the relevant CRH-rich zone.[4] However, later circuit studies showed that Y_1-mediated NPY signaling in the PVN and dorsomedial hypothalamus can suppress thermogenic and cardiovascular sympathetic outflow.[5] Human data also suggest that NPY can damp HPA output under some conditions: peripheral NPY administration in healthy young men reduced ACTH and cortisol while promoting sleep.[6] The literature therefore supports a circuit- and receptor-specific interpretation rather than a simple "NPY activates" or "NPY inhibits" model.

NPY also appears to shape the longer tail of stress physiology. In mice, acute stress induces durable adrenal sympathetic plasticity, and this change is attenuated when NPY/Y_1 signaling is disrupted.[7] Thus, NPY is not only an acute cotransmitter; it also participates in how previous stress exposure changes future autonomic responsiveness.

3 How the HPA axis and NPY shape autonomic output

The HPA axis and ANS are partially coupled but not identical stress systems. In healthy humans, pharmacologic HPA stimulation with metyrapone reduces heart-rate-variability (HRV) indices of vagal tone, whereas dexamethasone suppression has little effect on resting autonomic modulation.[8] In mid-life adults exposed to acute cognitive stressors, HRV-cortisol coupling is clearest in participants who show the expected rise–peak–fall cortisol trajectory and much weaker in atypical responders.[9] This matters clinically because autonomic hyperarousal can persist even when peripheral cortisol measures appear only modestly abnormal.

NPY helps explain why the relationship is complex rather than linear. Peripherally, NPY supports sympathetic vasoconstriction and can magnify cardiovascular stress responses. Centrally, the same peptide can either facilitate CRH-driven endocrine output or restrain sympathetic and thermogenic drive, depending on where and how it is engaged.[4, 5] A useful synthesis is that NPY acts less like a single on/off switch and more like a state-dependent stress modulator. In acute threat, it may assist the organism in mobilizing energy and maintaining vascular tone; after the threat, it may also contribute to recovery, stress buffering, or adaptive recalibration.

This framework also helps explain why chronic stress syndromes often show mixed phenotypes: altered cortisol feedback, sympathetic dominance, low vagal tone, and context-dependent changes

in circulating or cerebrospinal NPY can coexist. In practice, investigators should not assume that a single plasma cortisol value or a single peripheral NPY measurement fully captures the behavior of the integrated stress network.

4 Human evidence in stress, PTSD, and resilience

PTSD provides the clearest human disease model linking NPY, the HPA axis, and the ANS. Combat veterans with PTSD show elevated cerebrospinal fluid (CSF) CRH and higher CSF cortisol despite variable peripheral cortisol findings, suggesting that central neuroendocrine exposure can be abnormal even when blood-based measurements are less dramatic.[10, 11] NPY measurements tend to point in the opposite, resilience-related direction. In chronic combat-related PTSD, low CSF NPY was reported relative to healthy controls,[12] and, in a later comparison restricted to combat-exposed veterans, CSF NPY remained lower in those with PTSD than in trauma-exposed controls without PTSD; lower NPY also correlated with worse Clinician-Administered PTSD Scale scores and more intrusive symptoms.[13]

Peripheral studies are broadly consistent, although they also reveal an important nuance. Combat-related PTSD has been associated with lower baseline and blunted yohimbine-stimulated plasma NPY, with lower NPY linked to more severe hyperarousal and noradrenergic reactivity.[14] In contrast, during military survival training, higher stress-evoked plasma NPY correlated with better behavioral performance, less dissociation, and better apparent stress resilience.[15] A later study suggested that some reductions in baseline plasma NPY may reflect trauma exposure itself rather than PTSD diagnosis alone.[16] Taken together, these findings suggest that CSF NPY may be closer to the core pathophysiology, whereas plasma NPY may reflect a mixture of trauma load, autonomic activation, and individual resilience.

From an autonomic standpoint, the key implication is that low NPY signaling appears to track a state of poor stress containment: stronger sympathetic reactions, less efficient buffering of norepinephrine release, and less adaptive recovery after extreme stress. That pattern aligns with the clinical picture of PTSD, where exaggerated alarm reactions, autonomic hyperarousal, and disrupted stress recovery are common.

5 Interventions currently at the forefront

The intervention literature is most coherent when divided into three layers: direct NPY-targeted treatment, HPA-axis-targeted treatment, and ANS-directed neuromodulation.

5.1 Direct NPY-targeted treatment: early clinical translation

The most advanced direct NPY strategy is intranasal delivery for trauma-related disorders. In a phase Ib randomized crossover study in PTSD, a single intranasal NPY dose was well tolerated

up to 9.6 mg; higher doses were associated with a greater reduction in post-provocation Beck Anxiety Inventory scores than placebo.[17] This is important because it moves NPY from a resilience biomarker toward a candidate therapeutic.

Clinical translation remains early phase, however. A separate phase I/II trauma-prevention protocol in level-two trauma patients has been registered and proposes integrating autonomic and HPA biomarkers such as urinary norepinephrine and plasma ACTH, but the public ClinicalTrials.gov record located for this review was last updated in August 2019 and contained no posted results.[18] The direct NPY field is therefore promising but not yet mature enough to count as established treatment.

The translational challenge is obvious from the mechanistic literature: systemic or broadly distributed NPY signaling is unlikely to have uniform effects. The clinically useful version of NPY therapy will probably require careful control of dose, delivery route, timing, and perhaps eventual receptor selectivity.

5.2 HPA-axis-targeted treatment: the most mature clinical evidence

When the pathophysiology is overt hypercortisolism, HPA-axis intervention is already mainstream clinical practice. Endocrine Society and Pituitary Society guidance continue to treat surgery as first-line therapy for Cushing disease when a resectable pituitary source is present, with medical therapy used for persistent, recurrent, or nonsurgical disease.[19, 20]

Among pituitary-directed agents, pasireotide remains an established option. In a phase III trial, pasireotide reduced urinary free cortisol and ACTH-related biochemical activity and improved clinical features, although hyperglycemia was frequent and remains a practical limitation.[21] Among steroidogenesis inhibitors, osilodrostat and levoketoconazole are among the best-supported current agents. In LINC 4, osilodrostat normalized mean urinary free cortisol in 77% of patients at week 12 versus 8% with placebo, with durable responses after continuation.[22] Pooled analyses also show improvement in blood pressure and glycemic control, which is clinically relevant because excess cortisol often presents with a cardiometabolic and autonomic phenotype rather than a purely endocrine complaint.[23] In LOGICS, withdrawal from levoketoconazole caused loss of cortisol control in most placebo-switched patients, while continued drug exposure preserved response.[24]

Glucocorticoid receptor modulation is the next frontier. Mifepristone already has evidence for meaningful improvement in hyperglycemia, blood pressure, weight, and overall clinical status in endogenous Cushing syndrome, especially when surgery has failed or is not feasible.[25] Relacorilant has now produced positive phase III data in the GRACE study, where continued therapy better maintained hypertension control than placebo withdrawal.[26] For a literature review written in April 2026, relacorilant is best described as one of the most important near-term HPA-axis drugs to watch.

5.3 ANS-directed neuromodulation: adjunctive but mechanistically attractive

Because many patients manifest stress-system pathology as sympathetic overdrive, ANS-targeted interventions are gaining traction as adjuncts. In PTSD, randomized sham-controlled transcutaneous cervical vagus nerve stimulation (tcVNS) reduced heart rate and other sympathetic stress markers during traumatic script and mental stress exposure.[27] A subsequent pilot study suggested that tcVNS may also improve symptoms and blunt inflammatory stress responses over repeated use.[28] These studies do not directly target NPY, but they act on the same integrated stress network and may be particularly relevant when low HRV and hyperarousal dominate the phenotype.

The limitation is that tcVNS remains an adjunctive, emerging strategy rather than a fully standardized front-line treatment for stress-related disorders. Even so, it is one of the clearest examples of an intervention that tries to rebalance autonomic physiology directly instead of only treating downstream symptoms.

6 Synthesis and future directions

Three themes emerge from the literature. First, NPY is best understood as an integrator of stress physiology rather than as a single-pathway peptide. It participates in sympathetic cotransmission, vascular tone, central CRH regulation, and stress-induced plasticity. Second, the HPA axis and ANS should be measured together whenever possible, because endocrine and autonomic dysregulation do not move in perfect lockstep. Third, the therapeutic landscape is stratified by maturity: direct NPY therapy is innovative but early phase, HPA-axis treatment is clinically established in hypercortisolism, and autonomic neuromodulation is a promising bridge between mechanism and symptom control.

For researchers, the most compelling near-term agenda is biomarker-guided stratification. Studies that simultaneously track NPY, ACTH/cortisol, HRV, blood pressure, inflammatory markers, and symptom trajectories are likely to be more informative than single-marker studies. For clinicians, the most practical conclusion is that treatment should be matched to the dominant phenotype: direct cortisol-lowering or receptor blockade for true hypercortisolism, autonomic rebalancing for hyperarousal-dominant states, and investigational NPY-based therapy where available in trials. The long-term frontier is precision stress medicine, in which endocrine, autonomic, and peptide biomarkers help determine not only diagnosis but also the most rational biologic intervention.

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