

REVIEW ARTICLE

The neuropeptide Y–autonomic–cardiovascular axis in military traumatic stress: Molecular mechanisms and translational implications for brain–heart crosstalk

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Abstract

Military traumatic stress provides a distinctive human model for studying brain–heart crosstalk because it combines threat exposure, operational strain, sleep disruption, autonomic activation, endocrine stress responses, and cardiovascular load. Posttraumatic stress disorder (PTSD) in military and veteran populations is increasingly recognized not only as a psychiatric consequence of trauma but also as a condition associated with elevated cardiovascular vulnerability. However, the molecular mechanisms linking traumatic stress, autonomic dysregulation, and cardiovascular risk remain insufficiently defined. Neuropeptide Y (NPY), a stress-responsive neuropeptide widely distributed throughout central and peripheral tissues, may represent a key molecular node in this process. Centrally, NPY participates in fear regulation, anxiety modulation, stress recovery, and resilience. Peripherally, NPY acts as a sympathetic co-transmitter and influences vascular tone, endothelial function, myocardial remodeling, and cardiac electrophysiology. This review summarizes evidence supporting the NPY–autonomic–cardiovascular axis as a mechanistic framework for brain–heart maladaptation in military traumatic stress. We propose a dual-role model in which acute stress-related NPY mobilization, interpreted alongside separate central-circuit evidence, may support resilience and preserve performance under extreme stress, whereas chronic NPY dysregulation or excessive peripheral sympathetic NPY signaling may contribute to autonomic imbalance, vascular dysfunction, arrhythmia susceptibility, and long-term cardiovascular burden. Translationally, NPY should not be treated as a stand-alone biomarker. Its value will depend on integration with heart rate variability, catecholamines, inflammatory markers, genetic variation, wearable monitoring, deployment exposure, PTSD trajectories, and cardiovascular endpoints. Future longitudinal military cohort studies are needed to determine whether NPY predicts risk, serves as a marker of recovery, mediates autonomic maladaptation, or identifies modifiable intervention targets in brain–heart medicine.

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1. Introduction

Military traumatic stress provides a distinctive human context for studying brain–heart crosstalk because it combines psychological threat, repeated exposure to injury or death, sleep disruption, environmental strain, sustained physical demand, and delayed recovery within a single operational framework.¹ Combat exposure, rather than deployment alone, has been associated with new-onset posttraumatic stress disorder (PTSD) symptoms after military deployment, indicating that the traumatic component of military service has measurable neuropsychiatric consequences.² Operational stressors such as sleep disruption, heat, dehydration, and undernutrition further amplify this burden by impairing cognition, mood, and physiological function during simulated combat conditions.³ Military populations therefore offer a clinically and biologically relevant model in which central threat processing, autonomic regulation, endocrine stress responses, and cardiovascular load can be examined as interacting systems rather than as isolated outcomes. A multinational meta-analysis of 49 studies of personnel deployed to Iraq or Afghanistan estimated current PTSD prevalence at 12.9% after Iraq deployment and 7.1% after Afghanistan deployment; pooled prevalence was 12.4% in army, navy, and marine samples versus 4.9% in other services, but heterogeneity and concentration in Canadian, United States, and United Kingdom forces preclude interpretation as a worldwide prevalence estimate.⁴

The cardiovascular relevance of military traumatic stress is increasingly difficult to dismiss as secondary or incidental. PTSD has been associated with early-age heart disease mortality in Vietnam veterans, supporting the view that trauma-related psychopathology may contribute to long-term cardiovascular vulnerability.⁵ Twin data from Vietnam-era veterans further showed an association between PTSD and incident coronary heart disease, reducing the likelihood that this relationship is explained only by shared familial or genetic background.⁶ Large veteran cohorts have also linked PTSD with incident ischemic heart disease, atrial fibrillation, and stroke, suggesting that trauma-related cardiovascular vulnerability spans coronary, electrophysiological, and cerebrovascular domains.^{7–9} These findings support a brain–heart framework in which PTSD is not only a psychiatric diagnosis but also a marker of altered neuroautonomic and cardiovascular regulation.

Autonomic dysregulation is a plausible intermediate mechanism linking traumatic stress to cardiovascular risk. Meta-analytic evidence shows that PTSD is associated with elevated basal cardiovascular activity and heightened psychophysiological reactivity, consistent

with persistent hyperarousal and impaired physiological recovery.^{10,11} Heart rate variability (HRV) studies further indicate that PTSD is associated with autonomic dysfunction, particularly reduced autonomic flexibility and impaired parasympathetic regulation.¹² In active-duty Marines, lower predeployment HRV predicted greater postdeployment PTSD risk, suggesting that autonomic regulation may represent both a vulnerability marker and a mechanistic bridge between trauma exposure and later clinical outcomes.¹³ However, HRV and related autonomic indices describe physiological state but do not fully explain the molecular mediators that convert stress exposure into either adaptive resilience or maladaptive cardiovascular burden.

Neuropeptide Y (NPY) is a strong candidate molecular node within this brain–heart axis. NPY is a 36-amino-acid neuropeptide originally identified from brain tissue, and its receptor system is distributed across central and peripheral tissues relevant to stress regulation, autonomic control, and cardiovascular function.^{14,15} Central NPY signaling is implicated in anxiety, fear modulation, stress recovery, and PTSD-related vulnerability, while peripheral NPY acts as a sympathetic co-transmitter with effects on vascular tone, cardiac electrophysiology, endothelial biology, and myocardial remodeling.^{16–18} This dual anatomical and functional distribution makes NPY particularly relevant to neurocardiology because it can plausibly link central stress resilience with peripheral cardiovascular load.

Human military stress studies directly support this framework. During military survival training, plasma NPY increased under severe acute stress, and greater NPY responses were associated with better performance and lower subjective distress, suggesting that acute NPY mobilization may contribute to adaptive stress responses.^{19–21} In contrast, combat-related PTSD has been associated with lower baseline and yohimbine-stimulated plasma NPY levels, and cerebrospinal fluid NPY has been reported to be lower in PTSD, supporting the possibility that insufficient or dysregulated NPY signaling may contribute to chronic trauma-related maladaptation.^{22,23} These apparently divergent findings suggest that NPY should not be interpreted as simply protective or harmful; rather, its effect may depend on timing, compartment, receptor subtype, and degree of autonomic recovery.

This review examines the NPY–autonomic–cardiovascular axis as a molecular framework for brain–heart crosstalk in military traumatic stress. We first describe military traumatic stress as a human model of brain–heart interaction and summarize evidence linking PTSD to cardiovascular vulnerability. We then review the biological distribution, receptor signaling, and central stress-

regulatory functions of NPY, followed by its peripheral role as a sympathetic co-transmitter in cardiovascular regulation. Finally, we propose a dual-role model in which acute stress-related NPY responses, together with central circuit evidence, may support resilience, whereas chronic or excessive peripheral sympathetic NPY signaling may increase cardiovascular burden through autonomic imbalance, vascular dysfunction, myocardial remodeling, and susceptibility to arrhythmia. **Figure 1** shows the proposed NPY–autonomic–cardiovascular axis in military traumatic stress.

2. Military traumatic stress as a human model of brain–heart crosstalk

2.1. Characteristics of military traumatic and operational stress

Military traumatic stress should not be treated as a single psychological exposure, because combat deployment

combines perceived threat, witnessing death or injury, role-based operational demands, and barriers to postdeployment recovery.¹ Among the United States Army and Marine Corps personnel deployed to Iraq and Afghanistan, combat duty was associated with clinically significant mental health problems and with stigma-related barriers to care, indicating that military traumatic stress is shaped by both battlefield exposure and post-exposure institutional context.¹ Population-level postdeployment screening further showed that returning from deployment in Iraq or Afghanistan was associated with increased use of mental health services and attrition from military service, supporting the view that deployment stress produces both clinical and occupational consequences.²⁴

Prospective data from the Millennium Cohort Study refined this framework by showing that combat exposure, rather than deployment status alone, was associated with new-onset self-reported PTSD symptoms after deployment.² Sleep disruption represents a major

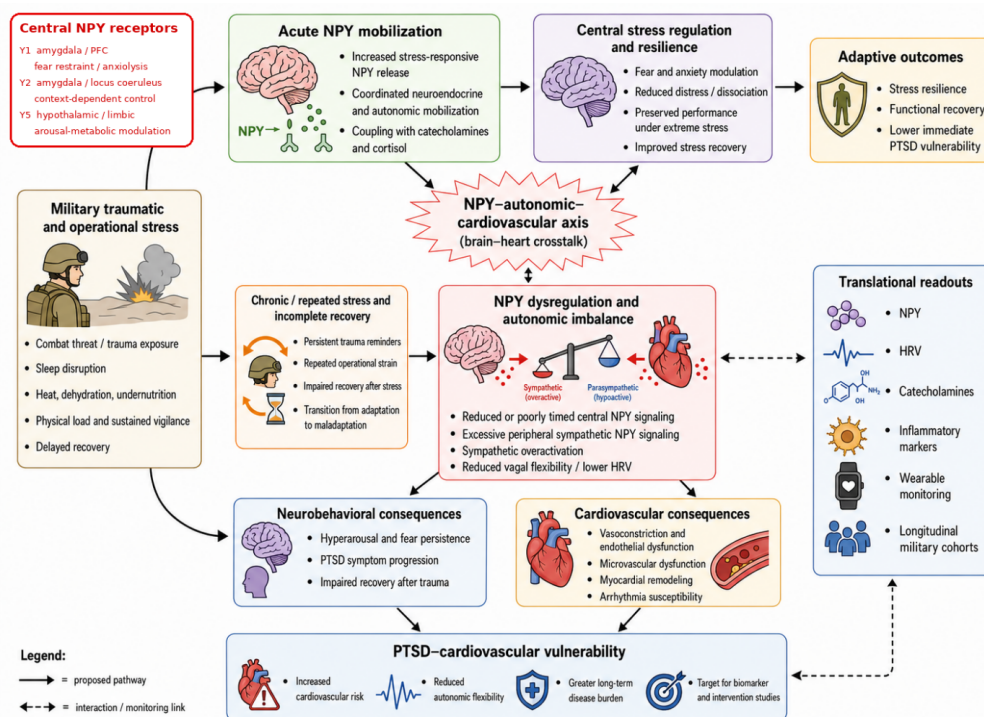


Figure 1. Proposed NPY–autonomic–cardiovascular axis in military traumatic stress. Military traumatic stress is proposed to engage NPY-related central and peripheral pathways that modulate autonomic and cardiovascular function. Acute stress-related NPY responses, considered together with central-circuit signaling, may support stress adaptation and resilience. Chronic stress exposure is associated with NPY dysregulation, autonomic imbalance, and increased peripheral sympathetic activity, contributing to PTSD symptoms and cardiovascular dysfunction. The model links neurobehavioral and cardiovascular outcomes through a shared NPY–autonomic axis. Solid arrows indicate proposed directional pathways supported by varying levels of evidence; dashed arrows indicate interactions and monitoring relationships. Graphic elements were generated using GPT Image 2 (OpenAI) through ChatGPT, and the authors assembled and edited the final figure in Microsoft PowerPoint.

Abbreviations: NPY: Neuropeptide Y; PTSD: Posttraumatic stress disorder.

operational component of military stress because service members reported altered sleep patterns before, during, and after deployment to Iraq and Afghanistan.²⁵ Simulated combat research also demonstrates that sleep loss, heat, dehydration, and undernutrition can jointly impair cognition, mood, and physiological function, indicating that military operational stress is a multisystem physiological burden rather than a purely psychological stressor.³ These features make military traumatic stress a useful human model for brain–heart crosstalk, as threat processing, sleep loss, metabolic strain, environmental stress, and delayed recovery converge on neural, autonomic, endocrine, and cardiovascular regulation.³

2.2. Posttraumatic stress disorder and cardiovascular vulnerability in military populations

Posttraumatic stress disorder in military and veteran populations should be regarded as a cardiovascular risk-relevant condition, not merely as a psychiatric endpoint, because prospective follow-up in Vietnam veterans showed that PTSD was associated with early-age heart disease mortality.⁵ The association between PTSD and coronary heart disease is strengthened by twin data from Vietnam-era veterans; PTSD was associated with incident coronary heart disease even in a design that partially controls for shared familial and genetic factors.⁶ In aging veterans, PTSD was also associated with incident cardiovascular disease, suggesting that trauma-related cardiovascular vulnerability can persist across the life course.²⁶

The cardiovascular relevance of PTSD is not limited to predominantly male veteran cohorts, because a large cohort study of women veterans found that PTSD was associated with incident ischemic heart disease.⁷ PTSD has also been linked to electrophysiological cardiovascular outcomes, as a prospective cohort study of young and middle-aged veterans reported an association between PTSD and early incident atrial fibrillation after adjustment for established atrial fibrillation risk factors and depression.⁸ Cerebrovascular vulnerability belongs in the same brain–heart framework, as young and middle-aged veterans with PTSD showed elevated risk for incident transient ischemic attack and ischemic stroke during long-term follow-up.⁹ Taken together, these findings support a model in which PTSD represents a trauma-related brain state with measurable downstream cardiovascular consequences across coronary, arrhythmic, and cerebrovascular domains.⁸

2.3. Autonomic dysregulation as a shared pathway between trauma and cardiac risk

Autonomic dysregulation provides a direct physiological bridge between traumatic stress and cardiovascular

risk because PTSD is associated with elevated basal cardiovascular activity.¹⁰ Psychophysiological meta-analysis further showed that PTSD is characterized by heightened heart rate and electrodermal responses at rest and during trauma-related provocation, supporting a sustained hyperarousal model of trauma-related autonomic activation.¹¹ HRV studies sharpen this mechanism; lower HRV reflects reduced autonomic flexibility and impaired parasympathetic regulation, both of which are relevant to cardiovascular vulnerability.¹²

Veteran twin data support the autonomic pathway by showing that PTSD was associated with impaired autonomic modulation, reducing the likelihood that the association is explained only by broad between-person differences.²⁷ Military prospective evidence is especially important because lower predeployment HRV in active-duty Marines predicted greater postdeployment PTSD risk, indicating that autonomic regulation may function not only as a consequence of trauma but also as a pre-existing vulnerability marker.¹³ A large active-duty Marine cohort also showed that HRV characteristics were related to posttraumatic stress, supporting the relevance of autonomic monitoring in military populations before overt long-term cardiovascular outcomes develop.²⁸ Therefore, autonomic dysregulation can be positioned as the intermediate physiological layer through which military traumatic stress and PTSD may increase cardiac workload, impair cardiovascular flexibility, and contribute to long-term cardiovascular risk.¹²

3. Neuropeptide Y as a molecular regulator of stress resilience and autonomic control

3.1. Biological distribution and receptor signaling of neuropeptide Y

Neuropeptide Y is a highly conserved 36-amino-acid peptide originally identified from porcine brain extracts, establishing NPY as a structurally defined neuropeptide rather than a nonspecific stress marker.¹⁴ Early receptor-mapping work showed that NPY and its receptor subtypes are distributed across both brain and peripheral tissues, supporting its relevance to both central stress circuits and cardiovascular regulation.¹⁵ The NPY receptor family is a multi-receptor system in which receptor subtypes can mediate distinct and sometimes opposing physiological effects.^{29–32}

Developmental and adult mapping in mice showed complementary and overlapping expression of Y1, Y2, and Y5 receptors in the central and peripheral nervous systems, indicating that NPY signaling is anatomically positioned to influence both neural and autonomic functions.²⁹ Regional analysis of Y-receptor subtype mRNAs in rat brain further

demonstrated that Y1, Y2, Y4, and Y5 receptor expression is brain-region-specific, providing an anatomical basis for receptor-subtype-specific effects on stress, feeding, emotional behavior, and autonomic output.³⁰ Convergent mapping data indicate that Y1 receptor expression is widespread in central neural networks relevant to neuroendocrine and behavioral regulation.^{29,30,32}

From a pharmacological perspective, NPY receptor ligands are considered therapeutically relevant because NPY receptors regulate anxiety, stress responses, energy balance, pain, epilepsy, and cardiovascular functions through receptor-subtype-specific mechanisms.³¹ In humans, the functional NPY receptor system is generally organized around hY1, hY2, hY4, and hY5 receptors, all of which belong to the G-protein-coupled receptor family and show subtype-specific ligand-recognition profiles.³² Therefore, this review frames NPY as a distributed neuropeptide signaling system rather than a single circulating biomarker, because its biological effect depends on compartment, receptor subtype, and central versus peripheral site of action.³² At a simplified circuit level, Y1 signaling in amygdala and prefrontal networks is generally linked to fear restraint and anxiolysis, whereas Y2 effects in the amygdala and locus coeruleus are context-dependent and may be anxiogenic or autoregulatory; Y5 is more prominent in hypothalamic and limbic modulation of arousal and metabolism.^{29,30,32–35} The receptor-level inset in [Figure 1](#) summarizes these central implications.

3.2. Central neuropeptide Y signaling in fear, anxiety, hyperarousal, and stress recovery

Central NPY signaling is strongly implicated in emotional regulation because early experimental work showed that NPY has anxiolytic-like effects mediated by Y1 receptors in the amygdala, with effects separable from hypothalamic feeding responses.¹⁶ Neurocircuitry-level evidence indicates that the amygdala, dorsal periaqueductal gray, lateral septum, and locus coeruleus participate in NPY-mediated anxiolytic-like effects, placing NPY within a distributed threat-processing and arousal-control network.³³ Amygdalar receptor-subtype studies further show that NPY signaling is not uniformly anxiolytic; Y2 receptor activation in the amygdala can mediate anxiety-like responses.³⁴

Conditional and site-specific experiments show that the central and basolateral amygdala are critical sites for NPY/Y2 receptor-mediated regulation of anxiety- and depression-related behaviors, reinforcing the importance of receptor localization for interpreting NPY effects.³⁵ Preclinical resilience studies further associate the NPY-ergic system with resistance to stress-induced behavioral dysfunction.³⁶ Fear-conditioning studies showed that

NPY modulates both the expression and extinction of fear-potentiated startle, supporting its role in learned threat responses that are relevant to trauma-related hyperarousal.³⁷

Intra-amygdala NPY infusion reduced conditioned fear in animal models, showing that local NPY signaling can directly modulate fear expression rather than merely altering generalized locomotor or motivational behavior.³⁸ Human PTSD data align with this central-deficit model; cerebrospinal fluid NPY concentrations were lower in patients with PTSD than in healthy comparison subjects.²³ High-intensity military survival training provides a directly relevant human stress model, because plasma NPY increased during severe training stress and was linked to stress-exposure phenotypes in healthy soldiers.¹⁹ In an animal model of PTSD, behavioral resilience to stress exposure was associated with the NPY-ergic system, supporting the interpretation of NPY as a resilience-linked stress modulator rather than only an anxiety peptide.³⁶ These findings support the central premise that deficient or poorly timed NPY signaling may contribute to fear persistence, hyperarousal, and impaired recovery after traumatic stress.³⁹

3.3. Peripheral neuropeptide Y as a sympathetic co-transmitter in autonomic regulation

Peripheral NPY is directly relevant to autonomic regulation because human surgical studies showed parallel increases in plasma NPY-like immunoreactivity and noradrenaline during sympathetic activation, supporting NPY as part of sympathetic vascular control in humans.¹⁷ Physiological activation studies in healthy humans showed that cold pressor exposure and exercise increased plasma NPY-like immunoreactivity alongside catecholamines, indicating that NPY can be released during ordinary sympathetic challenges rather than only during severe disease states.⁴⁰ Cardiac sympathetic stimulation in dogs produced coronary sinus overflow of both norepinephrine and NPY, directly demonstrating cardiac release of NPY during sympathetic neural activation.¹⁸

Neuropeptide Y also interacts with parasympathetic cardiac control, because experiments in human atrial tissue showed that NPY inhibits acetylcholine release through Y2 receptor activation.⁴¹ NPY can also act on cardiac endothelial biology; human endocardial endothelial cells express functional NPY-related responses that influence endothelial cell behavior.⁴² Cardiovascular reviews synthesize these findings by positioning NPY as a sympathetic co-transmitter involved in vascular tone, cardiac remodeling, angiogenesis, ischemia, arrhythmia, hypertension, atherosclerosis, and heart failure.⁴³

Clinical and experimental myocardial infarction data show that cardiac NPY release can be maladaptive under high sympathetic drive, as NPY promoted ventricular arrhythmogenesis after ST-elevation myocardial infarction despite beta-blockade.⁴⁴ In stable chronic heart failure, coronary sinus NPY levels predicted adverse outcomes, indicating that myocardial NPY may serve as a marker of hyperadrenergic cardiac stress and prognosis.⁴⁵ In ST-segment-elevation myocardial infarction, peripheral venous and coronary sinus NPY levels correlated with microvascular dysfunction and infarct size, supporting a mechanistic link between sympathetic co-transmission, coronary microvascular control, and myocardial injury severity.⁴⁶ These findings support a peripheral model in which NPY couples sympathetic activation to vascular resistance, vagal inhibition, endothelial signaling, arrhythmia susceptibility, and adverse cardiac outcomes.⁴³

4. The neuropeptide Y—autonomic—cardiovascular axis in brain–heart maladaptation

4.1. Acute neuropeptide Y mobilization as an adaptive response to military stress

Acute military stress should be interpreted as a coordinated neuroendocrine and autonomic mobilization rather than as a nonspecific psychological reaction, because survival training produces marked changes in cortisol, catecholamines, and other related stress hormones in healthy military personnel.⁴⁷ In this setting, NPY is especially relevant; higher NPY release during uncontrollable stress was associated with better human performance, suggesting that acute NPY mobilization may support operational adaptation under extreme threat.²⁰ The adaptive interpretation is strengthened by replication data showing that NPY was positively related to cortisol and norepinephrine during acute survival-school stress, while greater NPY release was associated with lower subjective distress.²¹

Acute military stress also includes physical and metabolic strain, and adrenal stress studies in Navy Survival, Evasion, Resistance, and Escape training show that catecholamines, cortisol, testosterone, and NPY change across stress and recovery phases rather than moving as a single uniform stress signal.⁴⁸ Stressful military training data further show that endocrine reactivity is linked to performance and psychological impact, supporting the broader claim that biological stress responses can index adaptive capacity during military selection or training environments.⁴⁹ Together, these military stress studies show that acute adaptation integrates endocrine, autonomic, cardiovascular, cognitive, and metabolic demands^{3,47–49}

The adaptive stress-mobilization model is not limited to NPY alone, because higher dehydroepiandrosterone sulfate-to-cortisol ratios during acute survival stress were associated with fewer dissociative symptoms and better objective performance.⁵⁰ These data indicate that coordinated endocrine balance, rather than a single hormone concentration, tracks dissociation and performance under acute military stress.⁵⁰ Together, these findings support a model in which acute NPY mobilization is part of a broader adaptive stress-response pattern that may preserve performance, reduce distress, and buffer autonomic overload during military traumatic or operational stress.

4.2. Chronic neuropeptide Y dysregulation and autonomic imbalance

Chronic brain–heart maladaptation may emerge when the acute adaptive NPY response becomes blunted, insufficient, or poorly coupled to noradrenergic activation. In combat-related PTSD, baseline plasma NPY and yohimbine-stimulated NPY responses were lower than in controls, while lower NPY was associated with greater noradrenergic and blood pressure reactivity, directly linking NPY dysregulation to autonomic hyperreactivity.²² Trauma exposure itself may contribute to this dysregulation, because reduced baseline plasma NPY was associated with trauma exposure rather than PTSD diagnosis alone in combat-exposed and active-duty samples.⁵¹ In combat-exposed veterans, plasma NPY concentrations were higher in those who had recovered from PTSD than in those with current PTSD, suggesting that restoration of NPY signaling may accompany recovery rather than merely reflect trauma exposure history.⁵²

Central NPY dysregulation is also evident in combat veterans; cerebrospinal fluid NPY concentrations were lower in combat-exposed veterans with PTSD than in combat-exposed veterans without PTSD and were negatively related to PTSD symptom severity.⁵³ Longitudinal combat cohort data further indicate that plasma NPY profiles differ in relation to posttraumatic stress symptoms, although peripheral NPY does not provide a simple one-directional biomarker of PTSD risk across cohorts.⁵⁴ This inconsistency is important as it argues against treating peripheral NPY as a stand-alone PTSD biomarker and instead supports a systems model in which timing, compartment, receptor signaling, and autonomic context determine the meaning of NPY changes.

Plasma and central NPY measurements are not interchangeable. Preclinical tracer studies in mice indicate measurable, nonsaturable entry of intact NPY from blood into brain, but its physiological relevance for human central signaling remains uncertain; human plasma

NPY disappears biphasically, with an initial half-life of approximately four min and a later phase of approximately 20 min.^{55,56} Circulating concentrations therefore depend on recent peripheral sympathetic release, sampling time, proteolysis, and clearance rather than directly reporting synaptic or regional brain NPY. Cerebrospinal fluid NPY is closer to the central compartment but still integrates production and clearance across regions. Validated human estimates of region-specific extracellular NPY clearance are unavailable; neither plasma nor cerebrospinal fluid therefore resolves local Y1/Y2/Y5 signaling or circuit-specific peptide turnover.^{23,32,39,53}

The clinical relevance of chronic NPY dysregulation extends beyond PTSD symptoms, because lower plasma NPY has been linked with suicidal behavior in combat veterans, suggesting that NPY-related stress regulation may also intersect with severe affective and behavioral outcomes.⁵⁷ Focused and systematic reviews likewise emphasize heterogeneous findings and the non-equivalence of central and peripheral NPY measures.^{39,58} A systematic review and meta-analysis found that NPY levels were lower in PTSD and major depressive disorder, whereas chronic stress findings were more heterogeneous, reinforcing the need to distinguish acute adaptive mobilization from chronic maladaptive dysregulation.⁵⁸ Therefore, chronic NPY dysregulation should be viewed as a failure of coordinated stress recovery and autonomic restraint rather than as a simple increase-or-decrease biomarker.

4.3. Neuropeptide Y-mediated vascular dysfunction, myocardial remodeling, and arrhythmia susceptibility

Peripheral NPY can contribute to cardiovascular maladaptation because it acts directly on coronary and vascular beds rather than only reflecting central stress biology. In patients with angina pectoris, intracoronary NPY infusion reduced coronary sinus oxygen saturation and produced prolonged coronary vasoconstrictive effects, showing that NPY can directly affect human coronary vascular function.⁵⁹ In acute ST-segment elevation myocardial infarction, NPY was associated with coronary microvascular constriction and reduced left ventricular ejection fraction, supporting a mechanism by which sympathetic co-transmission may worsen post-ischemic cardiac function.⁶⁰ Plasma NPY was also related to angiographic, electrocardiographic, and coronary physiology indices of reperfusion during ST-elevation myocardial infarction, indicating that NPY may mark or mediate impaired microvascular recovery after acute coronary occlusion.⁶¹

Neuropeptide Y also has growth-promoting vascular effects that are relevant to chronic vascular remodeling.

Experimental work identified NPY as an angiogenic factor from sympathetic nerves and endothelium, showing that NPY can stimulate endothelial cell migration, proliferation, and vessel growth at concentrations below those required for vasoconstriction.⁶² These trophic effects are context-dependent rather than uniformly maladaptive: Y2/Y5-linked angiogenesis can restore perfusion and function in ischemic tissue^{62,63}, whereas persistent Y1/Y5-associated smooth-muscle proliferation may favor neointimal remodeling and atherogenesis.^{64,65}

The adverse cardiac implications of NPY extend to prognosis and electrophysiology. Clinical prognostic evidence is strongest in hyperadrenergic cardiac states, where cardiac or circulating NPY is associated with adverse outcomes.^{45,46,66} Taken together, these data support a cardiovascular maladaptation model in which sustained or excessive peripheral NPY signaling may promote coronary vasoconstriction, microvascular dysfunction, vascular remodeling, atherosclerotic susceptibility, impaired myocardial recovery, and adverse prognosis.

4.4. The dual-role hypothesis: Central resilience versus peripheral cardiovascular burden

The central problem in interpreting NPY is that the same molecular system may support psychological resilience in the brain while increasing cardiovascular burden in the periphery. Preclinical work shows that intranasal NPY delivered before or immediately after traumatic stress reduced later PTSD-like behaviors in rats, supporting a central protective role when NPY reaches stress-regulatory circuits during the early posttrauma window.⁶⁷ Intranasal NPY also reversed anxiety- and depressive-like behavior in a single prolonged stress model, indicating that NPY can modify established stress-related behavioral impairment rather than only prevent acute fear responses.⁶⁸

The translational relevance of central NPY delivery is supported by a randomized dose-ranging study in patients with PTSD, where intranasal NPY was well tolerated, and higher doses were associated with anxiolytic effects after trauma-script provocation.⁶⁹ These findings support further study rather than clinical readiness, because route, timing, dose, and receptor targeting remain unresolved.⁶⁹ In female rats, intranasal NPY also reduced depressive-like behavior after single prolonged stress, suggesting that sex and dose may influence the behavioral effects of NPY-based intervention.⁷⁰

However, intranasal peptide delivery does not guarantee selective brain exposure. NPY is vulnerable to enzymatic degradation and mucociliary clearance; delivered dose varies with formulation, device, olfactory deposition, and nasal physiology, and the fraction reaching target brain regions is uncertain.⁷¹ Human intranasal NPY produced

very low but measurable systemic absorption and prolonged local vasoconstriction, indicating that peripheral leakage and cardiovascular effects require monitoring.⁷² Given the short plasma persistence of intact NPY described above⁵⁶, clinical development requires standardized formulation stability, deposition, brain/plasma pharmacokinetics, dose-response, and repeated-dose safety.

The dual-role hypothesis requires caution because central delivery studies do not imply that high peripheral NPY is uniformly beneficial. More recent preclinical work showed that intranasal NPY can produce sustained extinction of fear memory, reinforcing its potential value in central fear-recovery circuits.⁷³

Sex-dependent regulation also limits generalization. Reviews indicate lower basal NPY expression in several female brain regions and sex-dependent receptor expression or affinity.⁷⁴ In female single prolonged stress models, doses effective in males did not consistently prevent behavioral or locus coeruleus changes, whereas another study found benefit at a different dose and endpoint^{70,75}, indicating that sex, hormonal state, timing, and dose must be modeled explicitly. Human military evidence is additionally concentrated in younger males and predominantly in United States, Canadian, and United Kingdom cohorts.^{4,76,77} PTSD incidence and burden vary by age, sex, service, and race/ethnicity, but NPY-specific effect-modification data remain sparse. Future studies should prespecify sex, age, race/ethnicity, ancestry, service era, exposure type, and medication use, and test interactions rather than merely adjust for demographics.

Therefore, the most defensible model is not that NPY is simply protective or harmful, but that its effect depends on compartment, timing, receptor subtype, and physiological context. Acute or targeted central NPY signaling may enhance resilience, reduce fear persistence, and support recovery after traumatic stress, whereas chronic or excessive peripheral sympathetic NPY signaling may increase cardiovascular load through vasoconstriction, microvascular dysfunction, remodeling, and arrhythmogenic vulnerability. This dual-role hypothesis provides the mechanistic bridge for understanding how military traumatic stress can initially recruit adaptive NPY-mediated resilience but later shift toward NPY-linked brain–heart maladaptation when autonomic recovery fails.

5. Translational implications and future directions

5.1. Neuropeptide Y as a candidate biomarker for posttraumatic stress disorder–cardiovascular risk stratification

Neuropeptide Y should be considered a candidate

biomarker for PTSD–cardiovascular risk stratification only within a multimodal framework, because human NPY expression is partly genetically regulated and is linked to stress reactivity, emotional processing, and resilience-relevant phenotypes.⁷⁸ Functional variation in the NPY promoter rs16147 has been associated with prefrontal NPY gene expression and negative affect, suggesting that NPY-related risk stratification may need to incorporate genetic and neurobehavioral layers rather than rely only on plasma peptide concentration.⁷⁹

NPY genetic variation may also be relevant to autonomic risk phenotyping; the NPY promoter polymorphism rs16147 was associated with perceived stress and cardiac vagal outflow in humans.⁸⁰ In United States military veterans, the rs16147 promoter polymorphism was associated with resilience to cumulative traumatic stress, especially intrusive symptoms, supporting its potential value for trauma-resilience stratification in military cohorts.⁸¹ Given that these associations remain modest and incompletely replicated, genotype should be treated as a hypothesis-generating modifier rather than a validated stand-alone predictor.^{79–81}

The translational appeal of NPY comes from its ability to bridge psychiatric and cardiovascular biology, because translational PTSD reviews describe NPY as a stress-regulatory transmitter with relevance to fear, anxiety, resilience, and trauma-related pathology.⁸² For cardiovascular risk stratification, NPY should be evaluated alongside established cardiac biomarkers rather than in isolation; military veterans with PTSD showed abnormal cardiac biomarker profiles and higher mortality risk in a cardiovascular cohort.⁸³ Recent electrophysiology data strengthen the cardiovascular relevance of NPY, as baseline NPY levels predicted mortality in patients with electrical storm, suggesting that NPY may index sympathetic-arrhythmic cardiovascular vulnerability in high-risk cardiac states.⁸⁴ Therefore, the most defensible translational position is that NPY may contribute to PTSD–cardiovascular risk stratification as one component of a layered panel incorporating genotype, peptide levels, autonomic physiology, inflammatory state, and cardiovascular phenotype. Table 1 outlines the central and peripheral roles of NPY in military traumatic stress and cardiovascular regulation.

5.2. Integration of neuropeptide Y with heart rate variability, catecholamines, inflammatory markers, and wearable monitoring

Neuropeptide Y measurement will have greater translational value if integrated with HRV, because HRV provides a noninvasive index of autonomic regulation and can be quantified through time-domain, frequency-domain, and

Table 1. Central and peripheral roles of neuropeptide Y in military traumatic stress and cardiovascular regulation

Domain	Central/brain-related evidence	Peripheral/cardiovascular evidence	Translational interpretation and representative references
Military traumatic stress context	Trauma and operational stress create a combined neuroendocrine–autonomic load. Threat processing, PTSD vulnerability, and impaired recovery provide the clinical entry point for brain–heart crosstalk.	Autonomic activation and cardiovascular load link deployment stress to later cardiovascular vulnerability.	Use military cohorts as a human model for stress-related brain–heart coupling. ^{1–13,24–28}
NPY distribution and receptor signaling	NPY is a distributed neuropeptide system with receptor-subtype-specific actions. Y-receptor expression in stress-regulatory brain regions supports effects on anxiety, fear, and arousal.	Peripheral receptor expression allows NPY to affect autonomic and vascular regulation.	Interpret NPY by compartment, receptor subtype, and timing rather than as a single circulating marker. Plasma, cerebrospinal fluid, and regional receptor expression are not interchangeable. ^{14,15,29–35,55,56}
Central stress regulation and resilience	NPY modulates fear, anxiety, hyperarousal, and stress recovery. Amygdala and related threat-processing circuits mediate anxiolytic, fear–extinction, and resilience-related effects.	Central regulation can indirectly reduce downstream autonomic load.	Potential marker or target for resilience, PTSD vulnerability, and stress recovery phenotypes. ^{16,19,23,33–39,74,75}
Peripheral sympathetic co-transmission	NPY is co-released with norepinephrine during sympathetic activation. Peripheral NPY reflects brain–autonomic output during stress responses but is not a direct measure of regional brain signaling.	NPY contributes to vascular tone, vagal inhibition, endothelial signaling, and cardiac sympathetic effects.	Combine NPY with HRV and catecholamines to phenotype autonomic imbalance. ^{17,18,40–43,53,55,56,85–87}
Acute adaptive stress response	Acute NPY mobilization can occur during severe military stress. Higher acute NPY responses are linked with reduced distress, lower dissociation, and better performance under extreme stress.	Short-term sympathetic–neuroendocrine activation may support immediate adaptation.	Candidate indicator of acute stress resilience and operational performance under controlled assessment. ^{19–21,47–50}
Chronic dysregulation and PTSD vulnerability	Repeated or unresolved stress may produce blunted, insufficient, or mistimed NPY signaling. Lower or dysregulated NPY is associated with PTSD symptoms, impaired recovery, and severe affective outcomes.	Autonomic restraint may fail when NPY is poorly coupled to noradrenergic and cardiovascular responses.	Avoid treating peripheral NPY as a stand-alone PTSD biomarker; interpret within a multimodal panel. ^{22,23,39,51–54,57,58,74,82}
Cardiovascular maladaptation	Excessive peripheral sympathetic NPY may amplify cardiovascular burden. Central stress dysregulation may sustain sympathetic drive and reduce vagal flexibility.	NPY is linked to coronary vasoconstriction, microvascular dysfunction, vascular remodeling, arrhythmia susceptibility, and heart failure outcomes.	Angiogenesis may support ischemic revascularization, whereas prolonged smooth-muscle proliferation favors maladaptive remodeling. Supports PTSD–CVD risk stratification and monitoring of hyperadrenergic cardiovascular states. ^{43–46,59–66,83,84}
Intervention and monitoring framework	NPY-related pathways can be targeted indirectly through autonomic regulation or directly through receptor-specific approaches. Central NPY delivery and receptor-targeted strategies remain mechanistically relevant, mostly preclinical or early-phase.	HRV biofeedback, breathing interventions, sympathetic blockade, and vagal neuromodulation target different levels of the same axis.	Direct brain exposure, systemic leakage, and delivery variability require pharmacokinetic validation. Integrate NPY, HRV, catecholamines, inflammatory markers, wearables, and longitudinal cohort data. ^{67–75,88–94}
Longitudinal military cohort design	Repeated measures are required to distinguish risk prediction, recovery indexing, and causal mediation. Predeployment baseline biology can identify vulnerability before trauma-related outcomes develop.	Postdeployment autonomic, inflammatory, and cardiovascular endpoints clarify long-term brain–heart burden.	Prioritize prospective designs with NPY, HRV, inflammation, sleep, exposure severity, PTSD trajectory, demographic effect modification, and cardiovascular outcomes. ^{76,77,85–87,95–106}

Abbreviations: CVD: Cardiovascular disease; HRV: Heart rate variability; NPY: Neuropeptide Y; PTSD: Posttraumatic stress disorder.

nonlinear metrics.⁸⁵ HRV is especially relevant to brain–heart crosstalk, as neurovisceral integration models link vagally mediated HRV to regulation of affective, cognitive, endocrine, and cardiovascular processes.⁸⁶

Inflammatory markers should be included in the same panel because HRV is inversely associated with inflammatory markers in cardiovascular disease populations, supporting a physiological link between autonomic regulation and immune activity.⁹⁵ Large cohort data further support the vagal anti-inflammatory pathway, as HRV predicted circulating inflammatory marker levels, indicating that autonomic indices may capture immunoregulatory capacity relevant to PTSD–cardiovascular comorbidity.⁹⁶ PTSD-specific inflammatory evidence also supports multimodal assessment, with a systematic review and meta-analysis finding altered inflammatory markers in PTSD compared with controls.⁹⁷

Catecholamine measures should be considered when interpreting NPY, as central noradrenergic activity is altered in PTSD; cerebrospinal fluid norepinephrine concentrations were elevated and correlated with symptom severity in patients with PTSD.⁸⁷ Wearable monitoring can extend this biomarker framework from static clinic sampling to longitudinal physiology, because wrist-wearable HRV biomarkers identified adverse posttraumatic neuropsychiatric sequelae after traumatic stress exposure.⁹⁸ These data justify a future biomarker platform in which NPY is interpreted together with HRV, catecholamines, inflammatory markers, and wearable-derived recovery trajectories rather than as a single-point blood test.

Parallel advances in soft bioelectronics may improve future measurement and perturbation of this axis. Poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) microstructured electrodes combine mixed ionic–electronic conductivity, mechanical compliance, and cytocompatibility¹⁰⁷; related devices have enabled stable bidirectional electrophysiology in three-dimensional cardiomyocyte spheroids and chronic recording and stimulation in rat hippocampus.^{108,109} These platforms do not validate NPY mechanisms, but they could support synchronized neural and cardiac phenotyping in experimental brain–heart studies.

5.3. Potential interventions targeting the neuropeptide Y–autonomic–cardiovascular axis

Interventions targeting the NPY–autonomic–cardiovascular axis should be framed as strategies to improve autonomic recovery and reduce cardiovascular load, not simply as methods to increase or suppress NPY. HRV biofeedback is one plausible autonomic intervention, as a pilot study in veterans with PTSD found

that HRV biofeedback increased HRV and reduced PTSD symptoms.⁸⁸ Predeployment autonomic training may have preventive relevance, given that a randomized controlled trial tested HRV biofeedback and cognitive bias feedback interventions to reduce postdeployment PTSD symptoms in military personnel.⁸⁹

Briefly, low-session HRV biofeedback protocols may be practical for military and veteran systems, although the evidence remains pilot-level.^{88,90} A later three-session HRV biofeedback pilot study in veterans with PTSD showed feasibility and improvements in autonomic function, although home-practice adherence remained a limitation.⁹⁰ Breathing biofeedback may also complement trauma-focused psychotherapy because adjunctive breathing biofeedback hastened PTSD symptom reduction during cognitive behavioral therapy exposure procedures.⁹¹

Sympathetic modulation is another intervention route, as stellate ganglion block reduced PTSD symptom severity in a multisite randomized clinical trial of active-duty service members.⁹² Vagal neuromodulation is mechanistically relevant to the cardiovascular side of the axis; vagus nerve stimulation has been investigated in cardiovascular disorders and directly engages autonomic pathways regulating cardiac function.⁹³ NPY-receptor-directed approaches remain preclinical but conceptually important because an NPY Y1 receptor agonist modulated the development of PTSD-like behavior in rats, supporting receptor-specific NPY signaling as a future mechanistic target rather than an immediately available clinical intervention.⁹⁴ The safest translational conclusion is that HRV biofeedback, breathing-based autonomic training, sympathetic blockade, vagal neuromodulation, and NPY-receptor pharmacology should be tested as complementary approaches that target different levels of the same brain–heart regulatory system.

5.4. Methodological challenges and priorities for longitudinal military cohort studies

The main methodological priority is prospective longitudinal design, because military traumatic stress cannot be interpreted mechanistically without predeployment baseline measures and repeated postdeployment follow-up. The Marine Resiliency Study provides an appropriate design template, as it collected structured clinical, psychological, and biological data before deployment and at multiple postdeployment time points in approximately 2,600 Marines.⁹⁹ In the same research framework, predeployment plasma C-reactive protein predicted postdeployment PTSD risk, demonstrating that inflammatory biomarkers can be evaluated prospectively rather than only after PTSD has developed.¹⁰⁰

Gene expression studies in deployed Marines show both the promise and the limitations of peripheral biomarkers; blood-based gene expression predictors of PTSD risk and resilience were identifiable but required cautious interpretation due to sample size and replication needs.¹⁰¹ Postdeployment transcriptomic classification studies extended this approach by identifying blood-based gene expression biomarkers among deployed Marines, but their pilot design shows that biomarker panels require independent validation before clinical application.¹⁰² Chemokine profiling in United States military service members also supports multiplex immune assessment because candidate chemokines were associated with PTSD onset, risk, resilience, and stress response, but this type of panel needs standardized timing, replication, and integration with symptom trajectories.¹⁰³

Future cohort studies should combine biomarkers with clinical, neurocognitive, and digital measures, as predeployment risk prediction improved when biomarkers, self-reports, and neurocognitive functioning were modeled together in active-duty personnel deployed to Afghanistan.¹⁰⁴ Glucocorticoid biology should remain part of this design, as pre-existing high glucocorticoid receptor number in peripheral blood mononuclear cells predicted subsequent development of PTSD symptoms after military deployment.¹⁰⁵ Related prospective work showed that glucocorticoid receptor pathway components predicted PTSD symptom development, supporting pathway-level analysis rather than isolated biomarker testing.¹⁰⁶ Therefore, future military NPY studies should use repeated measures of NPY, HRV, catecholamines, inflammatory markers, sleep, deployment exposure, PTSD symptoms, and cardiovascular endpoints to determine whether NPY predicts risk, serves as a marker of recovery, mediates autonomic dysregulation, or identifies modifiable treatment targets.

6. Conclusion

Military traumatic stress is a useful human model for studying brain–heart crosstalk because it combines threat exposure, operational strain, sleep disruption, autonomic activation, endocrine stress responses, and cardiovascular load. PTSD in military and veteran populations should not be viewed only as a psychiatric consequence of trauma; it is also associated with broader cardiovascular vulnerability. Autonomic dysregulation provides a plausible physiological bridge between these domains. NPY may represent a key molecular node within this brain–heart framework. Its central actions are linked to fear modulation, anxiety regulation, stress recovery, and resilience, whereas its peripheral actions connect sympathetic activation

with vascular tone, endothelial function, cardiac electrophysiology, and myocardial remodeling. This dual distribution makes NPY particularly relevant to military traumatic stress, where acute adaptation and chronic maladaptation may coexist. The central argument of this review is that NPY has a context-dependent dual role. Acute stress-related NPY mobilization, interpreted alongside separate central-circuit evidence, may support resilience and preserve performance under extreme stress. In contrast, chronic NPY dysregulation or excessive peripheral sympathetic NPY signaling may contribute to autonomic imbalance, vascular dysfunction, arrhythmia susceptibility, and long-term cardiovascular burden. Translationally, NPY should not be treated as a stand-alone biomarker. Its value will depend on integration with HRV, catecholamines, inflammatory markers, genetic variation, wearable monitoring, deployment exposure, PTSD trajectories, and cardiovascular endpoints. Immediate priorities are to establish predeployment baselines and harmonized preanalytical protocols for intact NPY and its metabolites; pair serial plasma or cerebrospinal fluid measures with HRV, catecholamines, inflammation, sleep, and wearable data; prespecify sex-, age-, race/ethnicity-, medication-, and genotype-stratified analyses; and adjudicate cardiovascular endpoints across deployment and recovery. Embedded mechanistic trials should test whether successful autonomic or trauma-focused interventions normalize NPY trajectories and whether those changes predict cardiac benefit. These steps will distinguish risk prediction, recovery indexing, causal mediation, and treatment targeting.

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Further disclosure

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) solely for language polishing, grammar correction, and readability improvement. The AI-assisted tool was not used to generate scientific conclusions, analyze data, interpret findings, create references, or replace the authors' intellectual contribution. All AI-assisted output was critically reviewed and edited by the authors. The authors take full responsibility for the content, accuracy, originality, and integrity of the submitted manuscript.

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