International Journal of Research in Medical Sciences
Kumari B. Int J Res Med Sci. 2025 Dec;13(12):5575-5581
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20253744

Review Article

Genetic modulator of stress resilience and blood pressure regulation: insights from polymorphic variation

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Received: 01 November 2025
Revised: 05 November 2025
Accepted: 06 November 2025

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ABSTRACT

Neuropeptide Y (NPY) is a remarkably conserved neuropeptide distributed throughout the central and peripheral nervous systems, where it exerts broad influence over stress regulation and cardiovascular stability. While chronic stress typically contributes to increased blood pressure, a subset of individuals maintain normal levels despite similar stress exposure, suggesting the involvement of protective genetic factors within the NPY pathway. Variations in the NPY gene, particularly functional promoter polymorphisms such as rs16147 C>T and related haplotypes, appear to shape individual differences in stress responsiveness, sympathetic activation and emotional resilience. High-expression alleles are generally linked with reduced norepinephrine release, lower blood pressure and greater psychological stability under stress, whereas low-expression variants tend to enhance sympathetic tone and heighten vulnerability to anxiety and stress-related hypertension. Experimental studies reinforce the concept of NPY as a central sympathoinhibitory regulator, acting mainly through presynaptic Y_2 receptors within autonomic control centers. Recognizing these genetic influences offers valuable insight into why stress affects individuals so differently and opens new avenues for precision medicine. Genotypic profiling may ultimately aid in tailoring interventions for hypertension, anxiety and post-traumatic stress disorder. Moreover, pharmacological strategies targeting the NPY system such as Y_2 receptor agonists or agents that modulate epigenetic regulation, represents promising directions for future therapy. Continued longitudinal and translational research is essential to confirm causal mechanisms and to establish NPY as a clinically useful biomarker and therapeutic target in stress-related cardiovascular and neuropsychiatric disorders.

Keywords: Chronic stress, Haplotypes, Normotension, Neuropeptide Y, Polymorphism

INTRODUCTION

Chronic stress is increasingly recognized as a significant contributor to the development and progression of cardiovascular and psychiatric disorders, including hypertension, anxiety and post-traumatic stress disorder (PTSD).[1,2] Interindividual variability in stress responsivity and emotional resilience suggests a genetic basis underlying these differences. Among the candidate genes implicated, the (NPY) gene has emerged as a key modulator of stress-induced physiological and behavioral outcomes.[3] Recent advances in molecular genetics have identified several polymorphisms and haplotypes within the NPY gene that influence its expression and downstream effects on the autonomic nervous system and emotional regulation. These genetic variants are associated with differential sympathetic activity, stress hormone release and susceptibility to stress-related disorders.[4-6]

This review examines current evidence on the role of NPY gene polymorphisms and haplotypes in shaping stress resilience, emotional adaptability and blood pressure regulation. It further discusses the clinical implications of these findings, including the potential for genotype-informed interventions and emerging NPY-targeted therapeutic strategies.

NEUROPEPTIDE Y: STRUCTURE AND AMINO ACID COMPOSITION

NPY is a 36-amino acid peptide derived from a 97-residue precursor, prepro-NPY. Synthesized in the endoplasmic reticulum and processed via the Golgi apparatus, it is stored in dense-core vesicles. The peptide undergoes C-terminal amidation, a modification crucial for its bioactivity and adopts the conserved "PP fold", a characteristic structure shared with other members of the PP/NPY/PYY (Pancreatic Polypeptide, Neuropeptide Y and Peptide YY) family. This fold allows effective binding to Y-family G-protein-coupled receptors (GPCRs). The peptide is rich in tyrosine residues, hence the "Y" in its name and plays key roles in both central and peripheral regulation.[7]

Receptors and signalling

NPY exerts its effects via G_i/o coupled GPCRs, primarily Y_1, Y_2, Y_5 receptors in humans. Y_1, Y_2 and Y_5 displays high affinity for NPY while Y_4 prefers pancreatic polypeptide and Y_6 is non-functional in humans.[8] Y_1 receptors are mainly postsynaptic and found in the cortex, hippocampus and amygdala, modulating feeding, anxiety and stress-coping behavior.[9] Y_2 is typically pre synaptic, abundant in hippocampus, thalamus and hypothalamus, modulating neurotransmitter release, memory, circadian rhythms.[10] Y_5 is located in hypothalamus, hippocampus and cortex and is responsible for appetite and energy balance.[11]

Central and peripheral localization of NPY

The arcuate nucleus (ARC) and paraventricular nucleus (PVN) of the hypothalamus exhibit the highest levels of NPY expression. It is also present in the supraoptic and dorsomedial nuclei, amygdala, hippocampus (notably the dentate gyrus), cerebral cortex, locus coeruleus (LC), nucleus accumbens (NA) and nucleus tractus solitarius (NTS).[12] In the CNS, ARC neurons project to the PVN, dorsomedial hypothalamus (DMH) and preoptic area which are key hubs for neuroendocrine and autonomic regulation. In the hippocampus, NPY is expressed by GABAergic interneurons, involved in neurogenesis and stress resilience.[13]

Peripherally, NPY is co-stored with norepinephrine in sympathetic nerves and is found in the adrenal medulla, heart, kidneys, platelets and gastrointestinal tract, playing roles in vasoregulation, stress response and metabolic control.[14,15]

Release and processing

NPY is secreted from large dense-core vesicles and is frequently co-released with norepinephrine during periods of increased sympathetic nervous system activation, such as under stress. Enzymatic processing by dipeptidyl peptidase IV and aminopeptidases produces truncated NPY forms which alter receptor specificity by losing affinity for Y_1 receptors while retaining or enhancing activity at Y_2 and Y_5 receptors.[16]

PERIPHERAL FUNCTION: LINKING STRESS AND BLOOD PRESSURE

In stressful situations, NPY is released alongside norepinephrine, potentiating vasoconstriction and amplifying sympathetic tone. Unlike norepinephrine, whose vasoconstrictive effects are transient, NPY binds to vascular Y_1 receptors and sustains vasoconstriction, even after the adrenergic surge subsides.[17] This mechanism provides critical insight into how stress contributes to the onset of hypertension. However, in resilient individuals, central NPY action (particularly in the hypothalamus and brainstem) may counterbalance peripheral vasoconstrictive effects by dampening sympathetic outflow, thereby contributing to normotension despite chronic stress.[18] This duality i.e. central inhibition vs. peripheral excitation makes NPY a key neurochemical buffer in stress physiology.

NPY: A CENTRAL AND PERIPHERAL MODULATOR OF STRESS RESILIENCE AND CARDIOVASCULAR

Homeostasis

NPY, abundantly expressed in hypothalamic nuclei such as the ARC and PVN, acts as a central modulator of stress resilience. In key brain regions including the amygdala, hippocampus and NTS, NPY exerts anxiolytic effects via Y_1 and Y_2 receptors, suppresses the hypothalamic-pituitary-adrenal (HPA) axis by inhibiting corticotropin-releasing hormone (CRH) release, promotes hippocampal neurogenesis and dampens sympathetic outflow. The LC, a key regulator of sympathetic nervous system activity, is modulated by NPY, which dampens norepinephrine release and helps suppress excessive sympathetic output during stress. The NA, involved in reward processing and motivation, also contributes to emotional resilience under chronic stress. Meanwhile, the NTS, a crucial hub for autonomic and visceral sensory integration, plays a role in cardiovascular regulation, where NPY helps maintain vascular tone and stabilize blood pressure.[19,20] These central mechanisms foster emotional stability and prevent overactivation of stress pathways as summarised in table 1.

Peripherally, NPY is co-released with norepinephrine during stress, where it sustains vasoconstriction by acting on vascular Y_1 receptors, ensuring blood pressure maintenance during prolonged sympathetic drive.[21] It also offers cardiovascular protection by reducing endothelial permeability and modulating heart rate variability, acting as a buffer against stress-induced hypertension.[22,23] This dual action positions NPY as a key neurochemical link between effective stress coping and maintenance of normotension in chronically stressed individuals.[24]

NPY IN STRESS AND ANXIETY REGULATION: RECEPTOR-MEDIATED RESILIENCE

NPY functions as a potent endogenous anxiolytic, playing a key role in modulating the stress response. Under acute stress, NPY is co-released with norepinephrine in limbic areas like the amygdala and LC, rapidly acting to counterbalance excitatory neurotransmission. Chronic stress elevates NPY expression in regions such as the amygdala and hippocampus, enhancing resilience by dampening excitatory glutamate circuits.

Y_1 receptors, which are postsynaptic and prominently expressed in regions such as the basolateral amygdala (BLA), hippocampus and prefrontal cortex, contribute to anxiolytic effects by suppressing glutamatergic transmission and inhibiting CRH expression in PVN. This, in turn, dampens HPA axis activation and reduces adrenocorticotrophin hormone (ACTH) and cortisol secretion. At the same time, Y_2 receptors located presynaptically in the hippocampus and hypothalamus act as autoreceptors, suppressing the release of NPY and norepinephrine. This inhibitory action decreases neuronal hyperexcitability and supports the maintenance of neurogenesis in the dentate gyrus during stress exposure. In the LC, NPY reduces norepinephrine output through Y_1-mediated inhibition, buffering autonomic symptoms such as tachycardia and hypertension.[25-27] These are summarised in table 2.

Behavioral studies corroborate this: NPY knockout mice exhibit heightened anxiety and poor stress recovery, while NPY administration improves coping and emotional stability.[28] Clinical findings in PTSD patients further support NPY's role, with higher levels associated with better stress tolerance and reduced psychiatric symptoms.[29]

GENOMIC STRUCTURE AND FUNCTIONAL SIGNIFICANCE OF THE NPY GENE

The NPY gene, located on chromosome 7p15.3, encodes NPY, a highly conserved and abundantly expressed peptide in both the central and peripheral nervous systems of mammals. Its evolutionary conservation highlights its essential biological roles. In humans, the gene comprises four exons and three introns, reflecting a complex genomic organization that supports its critical regulatory functions. The peptide is initially synthesized as a prepro-NPY (~97 amino acids), which is then processed to pro-NPY and finally cleaved into mature NPY.[30]

Genetic variability in NPY: a basis for stress-resilient blood pressure regulation

It is well established that NPY is co-released with norepinephrine from sympathetic nerve terminals and adrenal chromaffin cells during stress, where it amplifies sympathetic outflow and contributes to stress-induced elevations in blood pressure. This mechanism may partly explain why many individuals exposed to chronic stress develop hypertension. Nevertheless, some individuals exhibit normotension despite being chronically exposed to stress. Emerging evidence suggests that this variability may be attributed to genetic polymorphisms and distinct haplotype variants within the NPY gene, which influence its expression and functional output.[5,31] Experimental studies in animal models have further substantiated the role of NPY genetic variants in modulating both stress reactivity and cardiovascular outcomes, underscoring the significance of NPY gene architecture in determining individual resilience to stress-induced hypertension.

NPY gene polymorphisms

Several single nucleotide polymorphisms (SNPs) in the NPY gene affect its expression and function. The SNP rs16147, situated in the promoter region of the NPY gene, has a C allele linked to increased NPY expression, which is associated with enhanced stress resilience and reduced stress reactivity. In contrast the T allele is associated with lower NPY expression and possibly higher vulnerability to anxiety and stress-related disorders.[31] Other variants of SNPs are also known. They are rs3037354 and rs16139 that have been studied in relation to obesity, hypertension and psychiatric traits.[32,33]

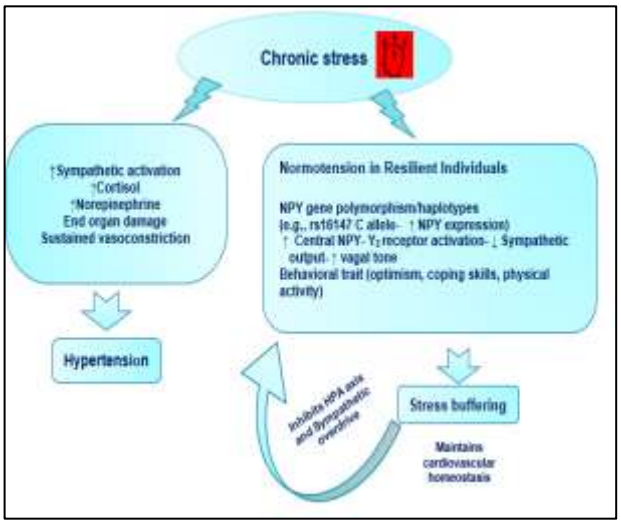

Figure 1: Why some individuals remain normotensive despite chronic stress.

Figure 1 summarizes the underlying mechanisms by which certain individuals remain normotensive despite chronic stress.

NPY gene haplotype

Certain haplotypes of NPY gene have been shown to significantly influence NPY expression and related physiological and behavioral traits. Zhou et al has identified three major NPY haplotypes labelled as H1, H2 and H3 based on common SNPs in the NPY promoter and untranslated regions. These haplotypes are functionally

distinct. Elevated NPY expression has been observed in association with the H1 and H2 haplotypes. H3 is associated with lower expression of NPY. Individuals carrying high-expression haplotypes (H1/H2) exhibit attenuated norepinephrine release in response to stress, which is associated with lower anxiety, enhanced emotional resilience and reduced blood pressure. Those with the low-expression haplotype (H3) tend to show greater stress reactivity, higher sympathetic tone and potentially increased risk for hypertension, PTSD and depression.[5]

NPY GENE VARIANTS AND NORMOTENSIVE RESPONSE TO CHRONIC STRESS: RESEARCH EVIDENCE

The capacity of certain individuals to remain normotensive despite prolonged stress exposure has drawn attention to the role of genetic variation in the NPY gene in modulating stress responses and cardiovascular homeostasis.

Human evidence: association of promoter variant rs16147 with parasympathetic tone

In a population-based study of 1,123 drug-free Han Chinese adults, Chang et al explored how the rs16147 (C>T) promoter SNPs influences cardiac autonomic responses to stress.[34] Using the Perceived Stress Scale (PSS) to stratify participants, those with high stress (PSS>21) and the T/T genotype demonstrated significantly higher heart rate variability (HRV) compared to C/C homozygotes, indicating superior parasympathetic (vagal) tone as summarised in Table 3.

The findings underscore a gene environment interaction, whereby the T allele, despite being associated with lower NPY expression, confers adaptive vagal regulation under chronic stress, suggesting a functional divergence in central versus peripheral NPY effects.[34]

Haplotype-specific effects: Zhou et al's landmark study

In a seminal study by Zhou et al involving 516 Finnish Caucasian participants, five common NPY haplotypes (H1–H5) were identified and their relationship with stress-related physiological responses was examined.5 Individuals with high-expression haplotypes (e.g., C-G-T) or C allele carriers at rs16147 exhibited higher NPY mRNA and peptide levels, blunted norepinephrine release, lower cortisol and blood pressure and greater emotional resilience.

In contrast, carriers of low-expression haplotypes (e.g., T-A-C) or the T allele exhibited elevated amygdala activation, increased sympathetic drive and markers of trait anxiety. Importantly, rs16147 alone accounted for a substantial proportion of interindividual variability in NPY expression, highlighting both composite haplotype and single-SNP contributions to stress physiology.[5] These findings are summarised in Table 4.

Temporal dynamics of plasma NPY levels in response to stress duration

An examination of plasma NPY patterns across various stress models reveals a time-dependent shift in its physiological role. Acute stress is associated with a transient rise in circulating NPY, supporting its sympathoinhibitory and vasoprotective functions . However, chronic stress leads to a decline in plasma NPY levels, suggesting systemic depletion or dysregulation. This adaptive-to-maladaptive transition reflects a breakdown of the NPY-mediated buffering system, potentially contributing to sustained sympathetic overactivity and elevated cardiovascular risk in chronically stressed individuals.[35]

Transgenic models: impact of NPY overexpression on blood pressure regulation

Transgenic animal models have provided critical insights into the physiological role of NPY in stress regulation and cardiovascular homeostasis. Studies using NPY-overexpressing transgenic rats by Michalkiewicz et al have demonstrated enhanced stress resilience, attenuated HPA axis activation and lower sympathetic nervous system outflow under chronic stress exposure. These animals exhibit reduced anxiety-like behaviours, lower circulating norepinephrine levels and protection against stress-induced elevations in blood pressure compared to wild-type controls.

Conversely, NPY knockout or under expressing models show heightened stress sensitivity, exaggerated sympathetic activity and increased susceptibility to anxiety and hypertension. These findings validate the functional relevance of NPY expression levels regulated by genetic variation in shaping the physiological and behavioral responses to chronic stress.[36] Transgenic rat models offer robust preclinical evidence connecting NPY expression to both emotional resilience and cardiovascular control, highlighting the clinical importance of NPY genetic variants observed in human studies.

Other relevant studies

There are few more experimental studies that have demonstrated the central sympathoinhibitory role of NPY, particularly via Y_2 receptor activation in specific autonomic brain regions such as the PVN and NTS.

According to Barraco et al and Cassaglia et al NPY-mediated activation of Y_2 receptors in the PVN and NTS inhibits excitatory neurotransmission, leading to a reduction in sympathetic output.[37,38] Studies by Casto et al and McLean et al demonstrate that central administration of NPY in the nucleus tractus solitarius and medulla oblongata modulates blood pressure by activating NPY-containing neurons, highlighting its role in the central regulation of cardiovascular function and hypotensive responses.[39,40]

Collectively, these findings from various studies underscore that NPY gene variants, both SNPs and haplotypes, modulate stress reactivity and cardiovascular adaptation, explaining individual differences in blood pressure responses to chronic stress. Central and peripheral NPY pathways interact dynamically, with genetic predispositions shaping the effectiveness of these stress-buffering mechanisms.

Targeting NPY signalling may represent a promising strategy in managing stress-related cardiovascular and psychiatric disorders. Despite growing evidence linking NPY genetics to stress resilience, most studies remain correlational. Longitudinal, multi-ethnic studies with larger cohorts and interventional designs are needed to establish causal pathways and therapeutic potential.

CLINICAL RELEVANCE

NPY is a pivotal modulator of the stress response, with established roles in enhancing emotional resilience, regulating appetite and offering neuroprotection across various neuropsychiatric and neurodegenerative disorders.[41] Its widespread expression and activity in both central and peripheral systems, position it as a promising therapeutic target for stress-related psychiatric conditions as well as cardiovascular diseases.

Genetic variations in the NPY gene, including SNPs and distinct haplotypes contribute to interindividual differences in stress adaptation, autonomic regulation and vulnerability to stress related disorders. These genetic insights offer a foundation for personalized medicine, where NPY genotypic profiling could inform risk stratification and guide targeted therapeutic strategies. Emerging avenues include the development of NPY-based pharmacotherapies, such as Y_2 receptor agonists or epigenetic modulators of NPY gene expression.[42,43] While promising, these approaches require rigorous validation in large, well-characterized cohorts before clinical translation. As research advances, integrating NPY profiling into clinical practice may enable more precise and effective management of stress-related and cardiovascular condition.

Table 1: Functional correlation of NPY with stress-coping brain centers.

Brain region	NPY function
Arcuate and paraventricular nucleus	Controls appetite, CRH release via HPA axis.[19,20]
Amygdala	Regulates fear and anxiety responses; NPY-Y_1 activation reduces anxiety.[19,20]
Hippocampus	Supports neurogenesis and cognitive resilience under chronic stress.[19,20]
Locus coeruleus	Modulates sympathetic output; NPY dampens norepinephrine release.[19,20]
Nucleus accumbens	Associated with reward, motivation and emotional resilience.[19,20]
Nucleus tractus solitarius	Autonomic and visceral sensory integration; NPY modulates cardiovascular tone.[19,20]

Legend: CRH- Corticotrophin releasing hormone, NPY: Neuropeptide Y, HPA-Hypothalamic- pituitary-adrenal.

Table 2: Receptor mediated action of NPY.

Target region	Receptor type	Action	Behavioural outcome
Amygdala (BLA)[25-27]	Y_1	↓ Glutamate, ↓ CRH	↓ Anxiety, ↓ Fear
PVN (Hypothalamus) [25-27]	Y_1	↓ CRH → ↓ ACTH & cortisol	↓ HPA Axis activity
Hippocampus[25-27]	Y_2	↓ Glutamate release, ↑ Neurogenesis	↑ Stress resilience
Locus Coeruleus[25-27]	Y_1	↓ Norepinephrine release	↓ Autonomic hyperarousal

Table 3: SNPs in the NPY gene affecting blood pressure.

Variant	Effect on NPY expression	Impact on stress and BP
C allele	Higher	Better stress buffering, lower BP, reduced anxiety.[34]
T allele	Lower	Heightened stress response, higher BP, increased risk of anxiety or depression.[34]

Table 4: SNPs and Haplotypes in the NPY gene affecting blood pressure.

Genetic feature	Specific variant/Haplotype	NPY Levels	Impact on stress and BP
SNP (rs16147)	C allele	High	Better stress buffering, ↓ BP, reduced anxiety.[5]
SNP (rs16147)	T allele	Low	Heightened stress response, ↑ BP, ↑ anxiety risk.[5]
Haplotype A	(e.g., C–G–T)	High	Calm under stress, ↓ cortisol, ↓ BP.[5]
Haplotype B	(e.g., T–A–C)	Low	High stress reactivity, ↑ BP and HR.[5]

FUTURE DIRECTIONS

Future research should focus on longitudinal cohort studies in humans to explore the dynamic relationships among NPY levels, catecholamines, blood pressure and NPY genotypes under conditions of chronic psychological stress. High-stress groups such as dementia caregivers, medical trainees, first responders, military personnel, individuals with PTSD and professionals in high-burnout occupations (e.g., air traffic controllers, nurses, teachers) serve as ideal populations for observing real-world stress adaptation.[29] These studies should incorporate repeated measurements of NPY, norepinephrine, epinephrine and cortisol in both plasma and cerebrospinal fluid, along with physiological indices such as blood pressure and heart rate variability (HRV). Concurrently, genotyping of key NPY variants (e.g., rs16147, rs16139) may help identify genetic contributors to stress resilience and autonomic regulation. In tandem, preclinical animal studies using targeted manipulation of NPY expression or receptor signalling are essential to elucidate underlying causal mechanisms. Together, these integrated clinical and experimental approaches could establish NPY as a predictive biomarker and therapeutic target for the personalized prevention and treatment of stress-related hypertension and associated disorders.

CONCLUSION

The cumulative evidence underscores the pivotal role of NPY gene polymorphisms and haplotypes in shaping individual responses to chronic stress. Individuals with low-expression variants or haplotypes, which constitute the majority of the population, demonstrate heightened sympathetic nervous system activity, elevated norepinephrine levels and are at greater risk for stress-related disorders such as hypertension, PTSD and depression. In contrast, a minority of individuals carrying high-expression NPY variants exhibit dampened adrenergic signalling, which contributes to lower blood pressure and increased stress resilience, even under prolonged stress. This protective phenotype is supported by both human genetic studies and animal models, highlighting the inhibitory role of NPY on sympathetic tone. Thus, polymorphic variations in the NPY gene provide a mechanistic explanation for interindividual differences in vascular and emotional responses to chronic stress, helping to clarify why some individuals remain normotensive and emotionally resilient despite enduring significant psychological burden.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kumari B. Genetic modulator of stress resilience and blood pressure regulation: insights from polymorphic variation. Int J Res Med Sci 2025;13:5575-81.