REVIEW ARTICLE

The neuroimmune–metabolic triad in cancer: Mechanistic links, carcinogen–neuropeptide interactions, and translational therapeutic insights

Mike Osagie Odigie[1], Lucky Omamuzo Ogagayere-Osagie[2], Kelvin Obakore Gbagbeke[2], Theophilus Tagun Dawus[3]*

[1]*Department of Physiology, Faculty of Basic Medical Sciences, College of Medical Sciences, Edo State University, Iyamoh, 312002, Edo State, Nigeria,* [2]*Department of Human Physiology, Faculty of Basic Medical Sciences, University of Delta, Agbor, Delta State, 321001, Nigeria*

[3]*Department of Anatomy and Cell Biology, Faculty of Basic Medical Sciences, College of Medical Sciences, Edo State University, Iyamoh, 312002, Edo State, Nigeria*

Abstract

The neuroimmune–metabolic triad is emerging as a critical integrative framework in cancer biology, linking neural signaling, immune modulation, and metabolic dysregulation. This review consolidates emerging insights into how neuropeptides such as substance P, neuropeptide Y, and CGRP can mechanistically intersect with carcinogen-triggered signaling networks in multiple tumor types. We dissect their roles in shaping the tumor microenvironment, influencing cytokine balance, immune cell plasticity, and metabolic stress responses. Particular emphasis is placed on translational implications: neuropeptides as dual-function biomarkers and druggable targets, and their relevance to immunometabolic reprogramming and treatment resistance. We critically evaluate single-cell spatial omics, brain–gut–tumor axis models, and ligand–receptor AI-mapping as tools to resolve triad interactions at high resolution. Finally, we propose a neuroimmune–metabolic roadmap for clinical exploitation; spanning early detection, therapeutic synergy, and personalized oncology. Framed within this conceptual model, the triad offers actionable insights for advancing cancer prevention, diagnosis, and therapy.

Keywords: neuropeptides, carcinogenesis, neuroimmune–metabolic triad, inflammation, metabolic reprogramming, tumor microenvironment

Introduction

Cancer as a neuroimmune and metabolic disorder

Although cancer is traditionally viewed as a disease driven by genetic mutations and uncontrolled cellular growth, accumulating evidence emphasizes its broader systemic dimensions; shaped by chronic inflammation, metabolic imbalance, and disruptions in neural signaling. Tumorigenesis is now recognized as the product of continuous interactions between the nervous system, immune pathways, and metabolic reprogramming within the Tumor Microenvironment (TME) [1, 2]. Hallmarks such as immune evasion, metabolic rewiring, and persistent low-grade inflammation do not occur in isolation; rather, they are orchestrated through complex regulatory networks, including those mediated by neuropeptides and their receptors [3].

Neuropeptides: Integrative regulators at the neural–immune–metabolic interface

Neuropeptides are small signaling molecules produced by neurons, immune cells, and endocrine tissues. Traditionally viewed as neuromodulators, many neuropeptides–including Substance P (SP), Neuropeptide Y (NPY), Vasoactive Intestinal

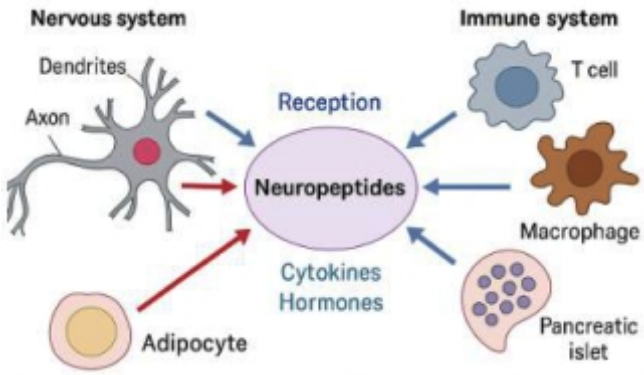

Figure 1: Neuropeptides as bridge for neural, immune, and metabolic systems

Peptide (VIP), and somatostatin—have now been implicated in immune regulation and metabolic homeostasis [4–6]. These molecules act as key integrators of homeostatic responses to stress, inflammation, and environmental stimuli.

Through their pleiotropic receptor systems, neuropeptides exert influence over cytokine release, immune cell recruitment, glucose metabolism, lipid storage, and angiogenesis; all of which are altered in tumor biology [7]. This central positioning allows neuropeptides to act as bidirectional messengers that bridge the Central Nervous System (CNS) with peripheral immune–metabolic circuits in cancer pathophysiology [8].

Carcinogens as neuroendocrine disruptors in oncogenesis

Environmental and lifestyle-associated carcinogens; ranging from tobacco smoke, polycyclic aromatic hydrocarbons, heavy metals, to endocrine disruptors, not only induce genotoxic damage but can also interfere with neuroimmune and neuroendocrine signaling pathways [9, 10]. These agents have been shown to alter neuropeptide expression profiles in brain regions and peripheral tissues, reprogram receptor sensitivity, and generate oxidative stress that perturbs synaptic and immune homeostasis [11]. For instance, carcinogen-induced neuroinflammation and altered neuropeptide signaling may contribute to a microenvironment conducive to immune tolerance and metabolic stress, thereby accelerating tumor initiation and progression [12].

Aim and Scope: Introducing the neuroimmune–metabolic triad as a translational framework

Given this multidirectional crosstalk, this review introduces and frames the neuroimmune–metabolic triad as a conceptual lens to understand how carcinogen exposure leads to coordinated disruptions in neuropeptide signaling, immune function, and metabolic homeostasis in cancer. We focus on mechanistic insights into how neuropeptides serve as molecular intermediaries linking these three axes, and examine their roles in tumor-specific contexts. This framework is not only timely but translationally relevant, as neuropeptide pathways are increasingly emerging as therapeutic targets and biomarkers across several cancer types. By mapping these interactions, we aim to bridge gaps between environmental oncology, neuroimmunology, and metabolic cancer biology, offering new opportunities for therapeutic innovation.

Carcinogen–neuropeptide interactions: Molecular disruption and pathogenic consequences

Overview of environmental and endogenous carcinogens

Carcinogenesis is driven not only by genetic mutations but also by persistent environmental, dietary, and lifestyle-related exposures that disrupt intercellular communication networks. Environmental carcinogens such as Polycyclic Aromatic Hydrocarbons (PAHs), nitrosamines, heavy metals (arsenic, cadmium), and air pollutants have been shown to affect not only genomic integrity but also neuroendocrine and immune signaling cascades [13, 14]. Endogenous sources, including Reactive Oxygen Species (ROS), microbial toxins, and lipid peroxidation byproducts (e.g., 4-HNE), contribute to a chronic inflammatory milieu that intersects with neuropeptidergic circuits [15]. Recent data suggest that several carcinogens act upstream of inflammation by perturbing neuronal and neuroendocrine regulatory hubs, thereby disrupting immune and metabolic homeostasis. These disturbances often manifest as sustained neuroimmune activation, Hypothalamic –Pituitary–Adrenal (HPA) axis dysfunction, and remodeling of neuropeptide signaling networks mechanisms, not traditionally foregrounded in cancer pathophysiology [16, 17].

Carcinogen-induced modulation of neuropeptide signaling

Several carcinogens have been shown to alter neuropeptide expression profiles either directly through transcriptional dysregulation or indirectly via inflammatory intermediates. For instance, benzopyrene exposure leads to increased SP expression and Neurokinin-1 Receptor (NK1R) upregulation in airway epithelium, facilitating pro-inflammatory cytokine release and tissue remodeling [18]. Heavy metals such as cadmium and mercury have been reported to affect hypothalamic levels of NPY, disrupting appetite and metabolic regulation with downstream oncogenic implications in tissues such as breast and colon [19]. *In vitro* models demonstrate that nitrosamine exposure modifies VIP and somatostatin secretion in gut epithelium, disrupting gut–immune signaling and barrier function factors; now implicated in colorectal tumorigenesis [20]. These observations support the hypothesis that carcinogens engage with neuropeptidergic pathways early in the disease trajectory, potentially preceding overt genomic damage or inflammation.

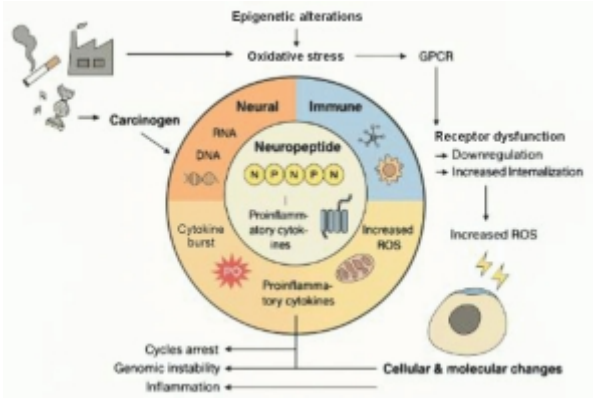

Figure 2: Molecular pathways of carcinogen-induced neuropeptide signaling disruption

Epigenetic and receptor-level disruption of neuropeptide genes

Epigenetic and receptor-level disruption of neuropeptide genes

Epigenetic alterations constitute a key mechanism by which carcinogens reprogram neuropeptide signaling. Promoter hypermethylation of the SST gene has been documented in various cancers, including pancreatic and lung tumors, correlating with reduced somatostatin expression and aggressive tumor phenotypes [21]. Similarly, histone deacetylation suppresses the expression of NPY in glioblastoma and prostate cancer, altering neuroimmune signaling within TME [22].

Carcinogen exposure also affects receptor expression and sensitivity. For example, upregulation of NK1R in response to chronic nicotine or alcohol intake enhances sensitivity to SP, amplifying neurogenic inflammation and vascular remodeling in preneoplastic lesions [23]. Moreover, alterations in G-Protein-Coupled Receptor (GPCR) trafficking and desensitization contribute to dysfunctional receptor recycling, further distorting neuropeptide signal fidelity [24].

Oxidative stress, neuroinflammation, and synaptic immune rewiring

Carcinogens frequently elicit oxidative stress–a primary trigger of neuroinflammation and synaptic remodeling. Elevated ROS and Reactive Nitrogen Species (RNS) compromise neuropeptide vesicular transport and synaptic release, disrupting neuroimmune communication across central and peripheral tissues [25]. Chronic oxidative injury alters neuronal excitability and glial activation patterns, particularly microglia and astrocytes, which can modify local neuropeptide gradients [26]. In the periphery, this manifests as immune cell desensitization, altered cytokine–neuropeptide cosignaling, and inappropriate activation of neuroimmune synapses. For instance, SP and CGRP dysregulation in inflamed mucosa have been implicated in aberrant macrophage polarization and fibroblast activation, contributing to carcinogen-driven mucosal malignancies [27].

Clinical relevance of disrupted neuropeptide – receptor binding in cancer

Aberrant neuropeptide–receptor interactions, shaped by carcinogen exposure are now recognized as clinically actionable events in oncology. Upregulated SP/NK1R signaling has been associated with poor prognosis in glioma, breast, and colorectal cancer, driving angiogenesis and epithelial– mesenchymal transition (EMT) [28]. Conversely, loss of SST/SSTR expression correlates with advanced tumor grade in neuroendocrine and gastrointestinal cancers [29]. Targeting these disrupted axes using NK1R antagonists (e.g., aprepitant), somatostatin analogs (e.g., octreotide), or VIP receptor modulators has shown promising results in preclinical and early clinical studies, offering a rationale for their integration into multimodal cancer therapy [30, 31]. These findings underscore the translational imperative to understand how carcinogen–neuropeptide interactions shape the tumorigenic landscape and influence therapeutic responsiveness.

Neuropeptides as bidirectional mediators of immune and metabolic dysfunction

Neuropeptides serve as integrative messengers linking neural input with immune surveillance and metabolic homeostasis. In the cancer context, this triadic communication becomes dysregulated, creating a permissive environment for tumorigenesis. Several neuropeptides through their specific GPCRs modulate inflammation, angiogenesis, cellular metabolism, and immune cell trafficking in ways that promote or suppress tumor growth depending on context, concentration, and receptor subtype engagement.

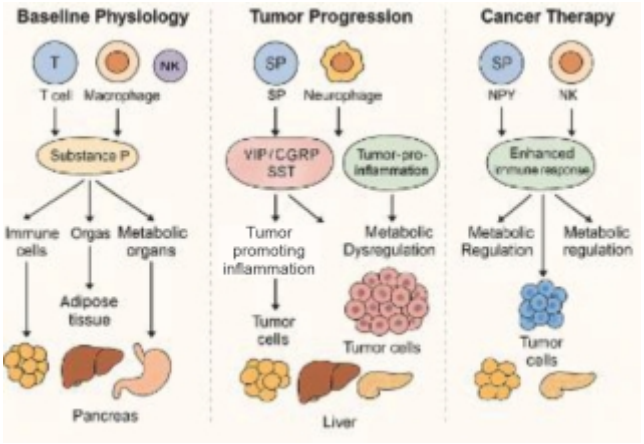

Figure 3: Bi-directional roles of neuropeptides in immune and metabolic modulation across cancer states

Substance P and NK1R: Inflammation, angiogenesis, and tumor progression

SP, a tachykinin family neuropeptide, exerts potent pro-inflammatory and angiogenic effects via its primary receptor, NK1R. Within the TME, SP–NK1R signaling promotes the release of interleukin (IL)-1β, Tumor Necrosis Factor-α (TNF-α), and Vascular Endothelial Growth Factor (VEGF), fostering chronic inflammation and neovascularization [32]. Upregulation of SP and NK1R has been detected in glioblastoma, breast, prostate, and colorectal cancers, where it correlates with tumor aggressiveness and reduced survival [33, 34]. Mechanistically, SP enhances proliferation, chemoresistance, and EMT through downstream activation of MAPK and PI3K–Akt pathways [35]. Pharmacological NK1R antagonists such as aprepitant have shown antiproliferative effects in preclinical models, suggesting therapeutic potential beyond their current antiemetic use [36].

Neuropeptide Y system: Immunosuppression and metabolic reprogramming

NPY, widely expressed in the hypothalamus and sympathetic nerves, regulates both energy homeostasis and immune suppression. In the cancer setting, NPY acts as an immunosuppressive modulator, inhibiting Natural Killer (NK) cell activity, reducing macrophage phagocytosis, and skewing dendritic cells toward tolerogenic phenotypes via Y1 and Y2 receptor engagement [37]. NPY also modulates lipid and glucose metabolism in tumors by promoting glucose uptake, lipogenesis, and adipokine release, creating a metabolically favorable niche for cancer progression [38]. Overexpression of NPY has been linked to poor prognosis in Ewing sarcoma, neuroblastoma, and breast cancer [39]. Importantly, metabolic reprogramming via NPY may confer resistance to standard therapies by fueling mitochondrial flexibility and autophagic survival [40].

VIP, CGRP, and tumor-promoting vasoregulation

VIP and Calcitonin Gene-Related Peptide (CGRP) are potent neurovascular regulators implicated in tumorigenesis through immune and endothelial modulation. VIP, acting through VPAC1 and VPAC2 receptors, suppresses pro-inflammatory cytokine release and promotes T-regulatory cell expansion,

thereby facilitating immune escape in tumors such as pancreatic, colorectal, and prostate cancers [41, 42]. Similarly, CGRP promotes vasodilation and angiogenesis while dampening macrophage and neutrophil activity [43]. In head and neck squamous cell carcinoma and melanoma, CGRP has been shown to promote tumor growth by enhancing vascular permeability and inhibiting cytotoxic T cell trafficking [44]. These findings highlight the double-edged role of vasoregulatory neuropeptides in shaping the TME toward immune evasion and nutrient influx.

Somatostatin: Tumor-suppressive and antiinflammatory roles

In contrast to other neuropeptides, somatostatin functions as a tumor suppressor and anti-inflammatory agent. Acting via five somatostatin receptor subtypes (SSTR1–5), it inhibits hormone secretion, angiogenesis, and cytokine release in a cell- and context-specific manner [45]. Downregulation or epigenetic silencing of somatostatin and SSTR2 have been observed in several malignancies, including pancreatic neuroendocrine tumors, colorectal cancer, and hepatocellular carcinoma [46]. Somatostatin analogs such as octreotide and lanreotide are approved for clinical use in Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs), where they prolong progression-free survival and exert antiproliferative effects [47]. Somatostatin also inhibits insulin and glucagon secretion, thereby influencing tumor metabolism, particularly in insulin-sensitive tissues [48].

Table 1: Key neuropeptides and their clinical roles in tumor-immune-metabolic dysregulation

Neuropeptide	Primary Receptors	Immuno-Metabolic Roles	Cancer-Associated Functions	Translational Relevance
Substance P (SP)	NK1R	Pro-inflammatory cytokine release, modulation of T-cell activity	Promotes tumor cell proliferation, angiogenesis, and migration in colorectal, breast, and gliomas	NK1R antagonists in clinical trials (e.g., aprepitant)
Neuropeptide Y (NPY)	Y1R, Y2R, Y5R	Regulates appetite, adipogenesis, and immune suppression	Enhances tumor growth, neoangiogenesis, and immune escape in breast, prostate, and neuroblastoma	Y1R/Y5R inhibitors under investigation
Vasoactive Intestinal Peptide (VIP)	VPAC1, VPAC2	Anti-inflammatory, vasodilatory, modulates glucose metabolism	Immunosuppression in tumor microenvironment; linked to lung and prostate cancer	VPAC receptor modulators in preclinical evaluation
Somatostatin (SST)	SSTR1–5	Inhibits hormone secretion, downregulates inflammatory mediators	Anti-proliferative, anti-angiogenic effects; diagnostic marker in neuroendocrine tumors	FDA-approved analogs (e.g., octreotide, lanreotide)

Continued...

Calcitonin Gene-Related Peptide (CGRP)	CALCRL/ RAMP1	Modulates nociception, inflammation, and vascular tone	Supports neurogenic inflammation, tumor-associated pain, potential role in brain tumors	CGRP-targeting therapies in migraine; potential in cancer pain control
Galanin	GALR1–3	Appetite regulation, modulates inflammation and insulin signaling	May contribute to tumor progression or suppression depending on receptor subtype	Galanin receptor subtyping under exploration for precision therapy
Orexins (Hypocretins)	OX1R, OX2R	Regulate arousal, energy homeostasis, and immune cell activation	Induce apoptosis in some tumors (e.g., colon, prostate); controversial effects	Selective orexin receptor agonists in drug development

NK1R: Neurokinin-1 Receptor; VPAC1/2: Vasoactive Intestinal Peptide Receptors; Y1R–Y5R: Neuropeptide Y Receptors; SSTRs: Somatostatin Receptors; GALRs: Galanin Receptors; OX1R/2R: Orexin Receptors

Neuropeptide interactions with insulin, leptin, and metabolic hormones in tumor metabolism

Neuropeptides not only mediate immune function but also intersect directly with metabolic hormones, notably insulin, leptin, ghrelin, and Glucagon-Like Peptide-1 (GLP-1). This crosstalk can amplify or dampen oncogenic metabolic rewiring. For example, SP and NPY have been shown to enhance insulin resistance, while leptin increases SP expression, forming a feedback loop that promotes inflammation and glycolytic metabolism in breast and colon cancer [49].

Similarly, somatostatin suppresses insulin and leptin signaling, potentially mitigating hyperinsulinemia-associated tumor growth. VIP, in contrast, enhances pancreatic insulin secretion and may support tumor proliferation via anabolic cues [50]. Such neuropeptide–hormone interactions can critically rewire tumor bioenergetics, alter systemic metabolism, and modify patient responses to treatment, particularly in obesity- and diabetes-associated cancers [21].

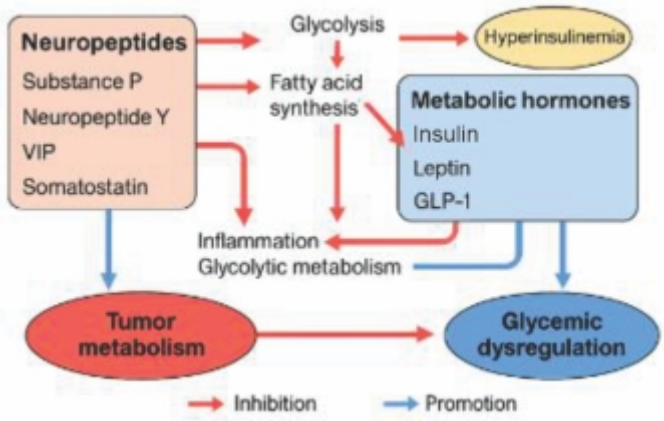

Figure 4: Schematic illustration of neuropeptide interactivity with insulin, leptin, and metabolic hormones in tumor metabolism

The neuroimmune–metabolic triad in carcinogenesis

Conceptualizing the triad: A systems-level view

Cancer development involves a convergence of dysregulated immune responses, metabolic perturbations, and neural inputs. This systems-level perspective introduces the *neuroimmune– metabolic triad*, a conceptual framework that positions neuropeptides at the interface of neural signaling, immune modulation, and metabolic regulation. Rather than functioning in isolation, these axes form a dynamic, interactive network that underlies the systemic milieu conducive to carcinogenesis. Disruption in neuropeptide signaling, whether by environmental carcinogens, epigenetic modifications, or receptor pathway reprogramming can simultaneously impact immune surveillance and metabolic homeostasis, ultimately skewing tissue microenvironments toward tumor-permissive states.

Carcinogen-induced neuropeptide pathways as immune modulators

Carcinogens such as polycyclic aromatic hydrocarbons, aflatoxins, heavy metals, and endocrine disruptors modulate neuropeptide signaling by altering gene transcription, post-translational processing, or receptor expression. This dysregulation compromises neuropeptides' immunomodulatory roles, including the inhibition or promotion of cytokine cascades, mast cell activa-tion, and leukocyte trafficking [22]. For instance, carcinogen-mediated upregulation of SP may promote chronic inflammation and angiogenesis, while suppression of VIP signaling can impair anti-inflammatory responses, facilitating immune evasion and tumor growth.

Metabolic dysregulation: Obesity, lipotoxicity, and insulin resistance

Metabolic dysfunction, including insulin resistance, adipokine imbalance, and lipotoxic stress, often accompanies or precedes oncogenic transformation. Neuropeptides such as NPY, somatostatin, and leptin-modulating peptides participate in regulating appetite, glucose metabolism, and lipid storage. Carcinogen-induced neuropeptide dysregulation may disrupt this delicate balance, fueling a metabolic phenotype that favors cellular proliferation, oxidative stress, and mitochondrial dysfunction; all key enablers of neoplastic transformation [35, 36].

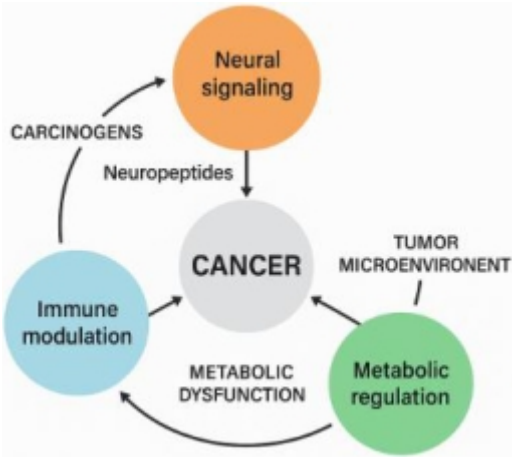

Figure 5: Neuroimmune–metabolic triad in carcinogenesis

Immune–metabolic reprogramming in the tumor microenvironment

Within the TME, immune and metabolic networks are reprogrammed by cancer cells to promote survival and expansion. Neuropeptides contribute to this remodeling by modulating T-cell polarization, macrophage phenotype switching (M1/ M2), and NK cell activity, while also regulating angiogenesis, hypoxia adaptation, and nutrient scavenging pathways [51]. SP, CGRP, and NPY are known to affect vascular permeability, immune cell infiltration, and glycolytic flux, linking neurogenic signaling with immunometabolic plasticity in the TME.

Interlocking feedback loops in tumor initiation and progression

The neuroimmune–metabolic triad does not operate linearly; rather, it is characterized by interlocking feedback loops. For instance, chronic inflammation elevates SP and CGRP, which in turn amplify cytokine production and vascular remodeling. Simultaneously, metabolic derangements such as hyperinsulinemia and adipokine excess further stimulate neuropeptide expression, closing a pathological loop that fosters tumor progression [52]. Breaking these circuits through neuropeptide receptor antagonism, metabolic correction, or immunomodulation, offers a promising translational opportunity.

Tumor-type illustrations of the triad in action

The molecular complexity of cancer is contextually shaped by tissue type, carcinogenic exposure, and neuroimmune–metabolic interactions. This section examines how the neuroimmune–metabolic triad manifests across selected cancers with varying environmental and endogenous risk factors.

Colorectal cancer: Carcinogens, microbiota, and neuropeptide modulation

Colorectal Cancer (CRC) presents a prototypic case where environmental carcinogens (e.g. dietary nitrosamines, heterocyclic amines) and gut-derived endotoxins converge on neuroimmune circuits. Neuropeptides such as SP, neurotensin, and VIP are dysregulated in response to epithelial barrier disruption and microbial dysbiosis, modulating colonic inflammation and tumorigenesis [53]. NK1R overexpression in CRC tissues correlates with increased proliferation and angiogenesis, potentially linking microbial-derived inflammation with SP-mediated oncogenic signaling [54]. Moreover, microbial metabolites such as butyrate modulate neuropeptide gene expression epigenetically, reinforcing the gut–brain–tumor axis [14].

Breast cancer: Adipose–neuropeptide crosstalk and immune escape

In breast cancer, metabolic dysfunction driven by adiposity establishes a permissive microenvironment for tumor progression. NPY, leptin, and Pro-Opiomelanocortin (POMC)-derived peptides are highly expressed in peritumoral adipose tissue, driving immunosuppression, estrogenic signaling, and metabolic reprogramming [55]. NPY–Y1R signaling modulates myeloid-derived suppressor cell recruitment and angiogenesis, while adipokine–neuropeptide interactions exacerbate insulin resistance and chronic low-grade inflammation [56]. The neuroimmune–metabolic feedback between breast adipose tissue and tumor cells exemplifies how neuropeptides orchestrate both local and systemic immune evasion.

Brain and lung tumors: Neurogenic inflammation and hypoxia-driven shift

Primary brain tumors (e.g. gliomas) and lung cancers demonstrate a convergence of neural plasticity, hypoxia, and neurogenic inflammation. SP and CGRP levels are elevated in peritumoral neural circuits and cerebrovascular beds, promoting vasodilation, immune cell trafficking, and Blood Brain Barrier (BBB) permeability [47]. In lung tumors, neuropeptides interact with Hypoxia Inducible Factors (HIFs) to enhance angiogenic and glycolytic pathways, with SP–NK1R and NPY–Y5R axes contributing to tumor cell invasiveness and macrophage polarization [55]. These malignancies illustrate how neuroimmune signaling under metabolic stress drives tumor aggressiveness.

Pancreatic cancer: Metabolic stress and neuropeptide dysregulation

Pancreatic Ductal Adenocarcinoma (PDAC) exemplifies the extreme end of tumor-associated metabolic dysfunction. Carcinogen exposure (e.g. smoking-related nitrosamines) and exocrine pancreatic insufficiency contribute to oxidative stress and neuroinflammatory responses that upregulate SP, VIP, and Neuropeptide FF (NPFF) [50]. These neuropeptides regulate fibrotic stromal remodeling, immune evasion, and insulin-glucagon imbalance in the tumor microenvironment [31]. Notably, VIP signaling may influence pancreatic β-cell exhaustion, reinforcing the bidirectional influence of tumor metabolism and neuropeptide-driven endocrine disruption [42].

Table 2: Tumor-type specific mechanisms illustrating the neuroimmune–metabolic triad

Tumor Type	Neuropeptide dysregulation	Immune dysregulation	Metabolic alterations	Key mechanisms and interactions	References
Colorectal Cancer	↑ SP, VIP, neurotensin; altered gut-brain peptide signaling	Gut microbiota-mediated TLR activation; chronic mucosal inflammation	Altered SCFA metabolism; epigenetic silencing of tumor suppressors	Carcinogen and microbiota-induced neuropeptide signaling via NK1R and VIPR promotes angiogenesis and immune evasion	[13-26]
Breast Cancer	↑ NPY, leptin–POMC interactions; upregulated Y1R/Y5R	Expansion of MDSCs, Tregs; estrogen-driven immune escape	Insulin resistance, increased leptin/adiponectin ratio, adipokine-driven inflammation	Adipose–neuropeptide axis fuels immunosuppressive, estrogenic, and metabolic crosstalk promoting tumor growth	[37-39]

Continued...

Brain Tumors	↑ SP, CGRP, VIP; BBB-permeable neuropeptides	Microglial activation; neurogenic inflammation; tumor-associated macrophages	HIF-driven glycolysis, mitochondrial reprogramming	Neuropeptide-driven vascular permeability, macrophage polarization, and hypoxia-adapted immunity	[40, 41]
Lung Cancer	↑ SP, NPY, VIP under hypoxia; elevated Y5R/NK1R	Tumor-associated neutrophils and macrophages; elevated PD-L1	Aerobic glycolysis; metabolic reprogramming via HIF1α	Hypoxia-induced neuropeptide signaling promotes immune escape and metabolic rewiring	[42]
Pancreatic Cancer	↑ SP, VIP, NPFF; disrupted β-cell–tumor signaling	Fibrotic stroma, T cell exclusion; M2 macrophage polarization	Lipotoxicity, β-cell dysfunction, glucagon–insulin imbalance	Carcinogen-driven inflammation triggers VIP/SP-mediated stromal remodeling and endocrine dysfunction	[43-45]
Blood Cancers (e.g., Leukemia, Lymphoma)	↑ SP, neurotensin, altered CNS–bone marrow neuropeptide axis	B cell receptor and TLR cross-talk; cytokine storm in acute cases	Altered glucose and lipid metabolism in hematopoietic niches	SP and NPY modulate bone marrow stroma, immune exhaustion, and hematopoietic metabolic demand	[46-48]

Targeting the neuroimmune–metabolic axis: translational strategies and therapeutic horizons

Neuropeptide receptor blockade (NK1R, Y1R, VIPR): Preclinical and clinical trials

Neuropeptide receptors represent tractable drug targets for modulating oncogenic signaling cascades. NK1R antagonist *aprepitant* has shown preclinical efficacy in inhibiting tumor growth in colorectal, pancreatic, and hematological cancers by antagonizing substance P-induced proliferation and angiogenesis [57, 58]. Similarly, Y1R antagonists, which counteract the tumor-promoting effects of NPY, have demonstrated immunostimulatory and anti-metabolic reprogramming effects in breast and prostate cancers [59]. Vasoactive Intestinal Peptide Receptors (VIPRs); notably VIPR1, are over-expressed in brain tumors and exhibit immuno-suppressive functions; early-phase trials using VIPR antagonists suggest potential for reversing tumor immune evasion [2].

Peptidomimetics and antagonists: Therapeutic development and safety profiles

Peptidomimetics; synthetic analogs of neuropeptides have emerged as promising agents due to enhanced stability and receptor selectivity. For example, NK1R -selective antagonists such as *fosaprepitant* and *netupitant* not only suppress tumor proliferation but also mitigate chemotherapy-induced nausea, thus offering dual therapeutic utility [50]. Developmental

focus now includes multi-receptor modulators targeting Y1R/VIPR interactions, although safety and off-target effects remain concerns. Importantly, neuropeptide-targeting agents show favorable tolerance profiles in initial human studies, encouraging broader investigation.

Epigenetic modulators of neuropeptide gene expression

Given the epigenetic dysregulation observed in neuropeptide gene promoters following carcinogen exposure, DNA Methyltransferase inhibitors (DNMTs) and Histone Deacetylase inhibitors (HDACis) offer a means of restoring normal neuropeptide signaling. For instance, HDACi treatment has been shown to upregulate somatostatin expression in colon cancer, exerting antiproliferative effects [51]. Moreover, epigenetic therapies may enhance receptor responsiveness to endogenous peptides, sensitizing tumors to adjunctive immunotherapy or metabolic agents.

Combinatorial approaches: Integrating immunotherapy and metabolic interventions

The bidirectional role of neuropeptides in immune and metabolic regulation supports combinatorial strategies. For example, checkpoint inhibitors (anti–PD-1/PD-L1) may be potentiated by neuropeptide receptor blockade, which reduces local immunosuppression. Concurrently, metformin, a metabolic reprogrammer, can synergize with neuropeptide antagonists to inhibit insulin/IGF-1 signaling pathways co-opted by cancer cells [59]. Such integrative paradigms targeting neuroimmune –metabolic nodes offer prospects for personalized, tissue-specific therapy.

Lifestyle, diet, and microbiome-based adjunctive therapies

Modulation of lifestyle factors can influence neuropeptide signaling. Dietary polyphenols (e.g., curcumin, resveratrol) modulate NPY and VIP expression and attenuate inflammation in preclinical models [60]. Microbiome-based interventions, including probiotics and prebiotics, alter gut-brain axis neuropeptide output and may reduce systemic inflammation and metabolic dysfunction; key features of the tumor-promoting environment. These low-risk, patient-accessible strategies complement pharmaceutical interventions in neuroimmune –metabolic cancer control

This table summarizes selected compounds that modulate neuropeptide-related signaling along immune and metabolic axes, either through direct receptor targeting, epigenetic control, or systemic modulation. It includes approved drugs, experimental compounds, and adjunct nutraceuticals with emerging roles in oncology.

Emerging models and tools to investigate neuropeptide–cancer networks

Single-cell and spatial multi-omics of the tumor –neuroimmune niche

Recent advances in single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have revolutionized the ability to dissect TME at single-cell resolution. These approaches uncover the cell-type-specific expression of neuropeptides (e.g., SP, NPY, VIP) and their receptors (e.g., NK1R, Y1R, VPAC1), alongside immune checkpoints, metabolic sensors, and epigenetic regulators within the neuroimmune–metabolic triad [54, 55]. Studies in breast and colorectal cancer have revealed spatially

restricted zones of neuropeptide–immune cell crosstalk, particularly near perivascular niches and hypoxic regions [26]. Coupling these datasets with proteomics and metabolomics enables integrative profiling of neuropeptide-driven metabolic rewiring and immune polarization across tumor types.

Brain–gut–tumor axis organoids and co-culture systems

Organoid systems derived from patient-specific tumors, intestinal epithelia, and neural crest–derived cells are enabling physiologically relevant investigations into brain–gut–tumor axis interactions [17]. Co-culture platforms combining tumor spheroids with enteric neurons, immune cells, or adipocytes allow for functional interrogation of neuropeptide-mediated modulation of cytokine release, epithelial-mesenchymal transition, and insulin resistance [18]. Organoid–microbiota models are especially useful in colorectal cancer to study butyrate-VIP interactions and SP-induced inflammation [19]. Despite their promise, standardization and reproducibility remain technical limitations.

AI and in silico models of ligand–receptor signaling

Artificial Intelligence (AI) and **machine learning** models have emerged as tools to decode the complexity of neuropeptide ligand–receptor signaling within the TME. Computational docking, network-based modeling, and dynamic pathway simulation platforms can predict interactions between neuropeptides (e.g., NPY, CGRP) and receptor isoforms under various metabolic or inflammatory states [30]. In silico tools are increasingly used to identify synergistic drug combinations targeting both neuropeptide receptors and immune/metabolic nodes, facilitating repurposing efforts (e.g., aprepitant with immune checkpoint inhibitors) [11]. Multi-omics integration powered by AI is crucial to prioritize biomarkers for translational validation.

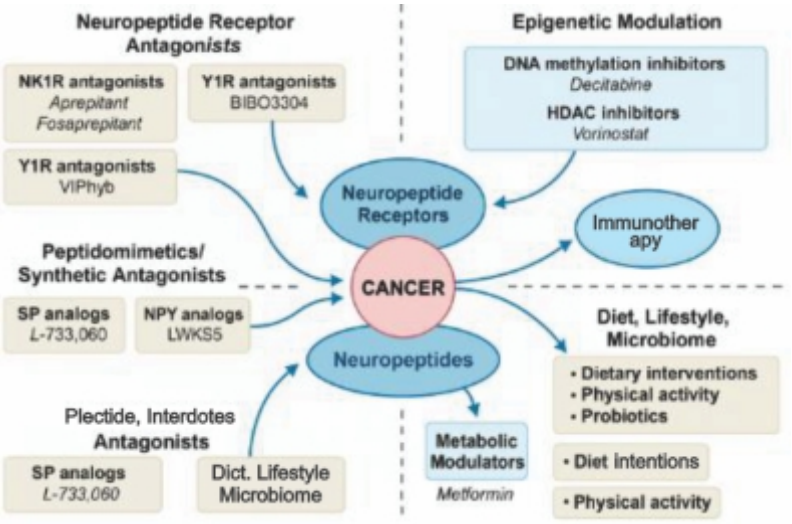

Figure 6: Therapeutic map of neuropeptide-targeted interventions in cancer

Table 3: Clinical and preclinical agents targeting neuropeptide–immune–metabolic pathways

Agent/ Class	Target	Mechanism of Action	Cancer Type(s)	Clinical Status
Aprepitant	NK1R (Substance P receptor)	Antagonizes SP–NK1R signaling, reducing proliferation, angiogenesis, and inflammation	Glioblastoma, breast, pancreatic	Approved (antiemetic); under cancer trials [34, 35]
L-822429	Y1R antagonist	Blocks NPY–Y1R signaling, modulates immune cell activity and stress response	Ovarian, prostate (preclinical)	Preclinical[34, 35]
Sr140333	NK1R antagonist	Inhibits SP-mediated MAPK and NF-κB activation	Pancreatic, colorectal	Preclinical [37]
VIP analogs (e.g., RO 25-1553)	VPAC1/2 receptors	Anti-inflammatory; promotes regulatory T cell activity; inhibits tumor-associated macrophages	NSCLC, melanoma	Phase I–II trials [38]
Somatostatin analogs (Octreotide, Lanreotide)	SST receptors (SSTR1–5)	Inhibits GH/IGF-1 axis, angiogenesis, and immune dysregulation	Neuroendocrine tumors	Approved [49]
Valproic acid	HDAC inhibitor	Epigenetic modulation of neuropeptide gene expression; enhances T cell activity	Breast, glioma	Phase II trials [50]
Butyrate (microbiota-derived)	GPR41/43, epigenetic pathways	Enhances VIP/NPY expression via gut–brain–immune axis; anti-inflammatory	Colon, liver	Nutritional/adjunctive [51]
Melatonin	Multi-target (immune-metabolic modulation, neuropeptides)	Restores circadian neuropeptide rhythms, antioxidant, modulates leptin/insulin signaling	Breast, prostate	Phase II–III trials [52]
Palmitoylethanolamide (PEA)	PPAR-α agonist, neuroimmune modulator	Inhibits neurogenic inflammation, SP and CGRP release	Glioma, neuroblastoma (preclinical)	Nutraceutical; early trials [53]

Neuroimmune humanized mouse models and translational relevance

Humanized mouse models that mirror the neuro-immune–metabolic interface are critical for robust preclinical assessment. Immunodeficient or human cytokine knock-in strains, when reconstituted with human hematopoietic stem cells and patient-derived tumor grafts, enable detailed evaluation of human-specific neuropeptide–immune interactions (such as NK1R–T-cell signaling and VIP-driven M2 macrophage polarization) [11,13]. Brain tumor platforms incorporating restored vagal or sympathetic innervation further elucidate neurogenic inflammatory pathways implicated in glioma and lung cancer progression. Nonetheless, cross-species discrepancies in neuropeptide receptor profiles remain a major constraint on the translational fidelity of these models

Limitations and barriers to clinical translation

Despite mechanistic clarity from preclinical models, the clinical translation of neuropeptide-targeted interventions faces key hurdles. First, the pleiotropic roles of neuropeptides across homeostatic and pathological contexts challenge selective targeting without off-target effects [34]. Second, redundancy and compensation among neuropeptide families (e.g., overlapping effects of VIP and PACAP) may dampen monotherapeutic efficacy. Third, inter-patient heterogeneity, especially in tumors influenced by obesity or microbiota, complicates biomarker-driven patient stratification. Finally, regulatory pathways governing the classification of neuropeptide-targeting compounds; ranging from nutraceuticals to peptidomimetics, remain poorly harmonized globally.

Table 4: Experimental models for investigating neuropeptide–immune–metabolic interactions in cancer

Model/System	Key Features	Neuropeptide Targets	Applications	Limitations	References
Single-cell RNA-seq + spatial transcriptomics	High-resolution mapping of cell types and ligand–receptor expression; spatial architecture retained	SP/NK1R, NPY/Y1R, VIP/VPAC1	Mapping tumor–neuroimmune niches; identifying therapeutic targets	Cost, data integration complexity	[15, 16]
Brain–gut–tumor axis organoids	Co-culture of intestinal epithelium, tumor cells, microbiota, neurons	VIP, NPY, CGRP, PACAP	Colorectal and pancreatic tumor studies; microbiota–neuropeptide signaling	Standardization, reproducibility	[17–18]

Continued...

Multi-omics AI platforms	Integrates genomics, proteomics, metabolomics with ligand–receptor inference	All neuropeptide classes	Predictive modeling of neuropeptide–receptor signaling; drug target prioritization	Requires curated datasets and validation	[21]
In silico docking & pathway simulators	Predicts binding affinities, downstream signaling cascades	NK1R, VPAC1, Y1R	Drug screening; mutation impact analysis	Lack of full biological context	[22]
Humanized mouse models (neuroimmune-competent)	Engrafted with human immune system and tumors	SP, VIP, NPY pathways	Functional validation of neuropeptide–immune interactions; drug testing	Species-specific neuropeptide differences; high cost	[23]
Neuronal co-culture systems with tumor spheroids	2D/3D models combining tumor cells with autonomic neurons	CGRP, SP, NPY	Investigating neurogenic inflammation and perineural invasion	Limited systemic interactions	[24]

SP = Substance P, VIP = Vasoactive Intestinal Peptide, NPY = Neuropeptide Y, CGRP = Calcitonin Gene-Related Peptide, PACAP = Pituitary Adenylate Cyclase-Activating Polypeptide

Future directions and open questions

The neuroimmune–metabolic triad represents a powerful conceptual framework for dissecting carcinogenesis across molecular, cellular, and systemic levels. However, several open questions remain that can shape the next decade of cancer research and therapy:

Can neuropeptide signatures predict carcinogen susceptibility?

Given their responsiveness to environmental stimuli, neuropeptides may serve as early biosensors of carcinogenic exposure. For instance, upregulation of SP or NPY has been observed in response to stressors and toxins, preceding overt oncogenesis [25, 26]. Integrating neuropeptide profiling into exposome-wide association studies could offer new insights into susceptibility and inter-individual risk variability.

Biomarker potential for early detection and risk stratification

The secretory and measurable nature of neuropeptides makes them attractive candidates for non-invasive cancer biomarkers. Recent efforts have identified plasma SP, VIP, and CGRP levels as correlates of tumor burden or progression in colorectal, lung, and neuroendocrine cancers [27-29].

However, systematic validation in large, longitudinal cohorts is necessary to distinguish causative patterns from reactive changes.

Sex, age, and epigenetic variability in neuropeptide-driven tumorigenesis

Hormonal and epigenetic differences between sexes and age groups may significantly alter neuropeptide receptor expression and downstream effects [30, 31]. For example, estrogen modulation of NPY and VIP pathways may underlie gender-specific cancer risks or treatment responses. Personalized oncology models should account for these demographic factors in trial designs and therapeutic development.

Designing precision oncology trials for neuropeptide–targeted therapies

Despite preclinical promise, neuropeptide antagonists (e.g., NK1R, Y1R blockers) remain underutilized in oncology trials. Precision stratification based on receptor expression, neuropeptide levels, and immune –metabolic profiles could enhance trial success. Moreover, peptidomimetics and multi-target drugs offer new avenues to integrate neuropeptide modulation with existing immunotherapies and metabolic interventions [32, 33].

Integrating the triad into cancer prevention and risk-reduction frameworks

The triad framework opens new opportunities for preventive oncology. Dietary modulation of the gut–neuropeptide axis, stress reduction, and metabolic correction (e.g., insulin sensitizers, microbiome interventions) could be repurposed for early-stage interventions or high-risk populations [34]. Risk models incorporating neuropeptide biomarkers, environmental exposures, and metabolic phenotypes may offer more holistic preventive tools

Conclusion

The convergence of neuropeptide signaling, immune modulation, and metabolic reprogramming constitutes a triadic axis that increasingly defines the landscape of carcinogenesis. This review establishes the neuroimmune–metabolic triad as a systems-level framework that unites disparate molecular events into a cohesive model of cancer pathogenesis. By elucidating how carcinogens perturb neuropeptide pathways to disrupt immune and metabolic homeostasis, we highlight under-recognized mechanisms that are both pathogenic and potentially targetable. Critically, the translational relevance of this triad is underscored by emerging therapeutic agents; ranging from neuropeptide receptor antagonists and epigenetic modulators to combinatorial immunometabolic strategies and microbiome-informed interventions. Case studies across colorectal, breast, brain, lung, pancreatic, and hematologic cancers further reveal how this integrative model manifests in tumor-type-specific contexts. As the oncology field moves toward precision and prevention, embracing neuropeptides as both biomarkers and therapeutic nodes offers a promising direction. Bridging neuroscience, immunology, and metabolic medicine, the neuroimmune–metabolic axis represents a new frontier for interdisciplinary collaboration in cancer research and clinical practice. Future investigations should prioritize translational modeling, demographic variability, and early-stage trials to fully realize the triad's diagnostic and therapeutic potential.

Funding

No specific grant was allocated by any agency, be it public, commercial, or non-governmental for this review.

References

1. Pratinidhi A, Chaugule P, Joshi R, Vhawal V, Mane D, Pawar B, *et al*. Effectiveness of cancer literacy activities in motivating rural men of Satara district for screening of oral cancers. *J Krishna Inst Med Sci Univ* 2022; 11(3):78–85.
2. Batlle E, Massagué J. Transforming growth factor-β signaling in immunity and cancer. *Immunity* 2019; 50(4): 924-940.
3. Sinha P, Kapoor S, Kadam SS, Sahu NK, Jaiswal AK. Potential therapeutic modalities in cancer gene therapy. *J Krishna Inst Med Sci Univ* 2017; 6(2):3-18.
4. Delgado M, Ganea D. Vasoactive intestinal peptide: a neuropeptide with pleiotropic immune functions. *Amino Acids* 2013; 45(1):25–39.
5. Sánchez ML, Rodríguez FD, Coveñas R. Neuropeptide Y peptide family and cancer: antitumor therapeutic strategies. *Int J Mol Sci* 2023; 24(12): 9962.
6. Mardelle U, Bretaud N, Daher C, Feuillet V. From pain to tumor immunity: influence of peripheral sensory neurons in cancer. *Front Immunol* 2024; 15:1335387.
7. Arabshahi S. Detection of polyomaviral large T antigen in benign prostatic hyperplasia and prostate carcinoma tissues. *J Krishna Inst Med Sci Univ* 2015; 4(1):28–33.
8. IARC Working Group. Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances. *IARC Monogr Eval Carcinog Risks Hum* 1999; 73:1–674.
9. Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect* 2000; 108(Suppl 3):511–33.
10. De Felice FG. Alzheimer's disease and insulin resistance: translating basic science into clinical applications. *J Clin Invest* 2013; 123(2):531-539.
11. Gupta N, Nagar A. Giant mucinous cystic neoplasm of pancreas in an elderly female: a rare case report. *J Krishna Inst Med Sci Univ* 2023; 12(2):134–137.
12. IARC Working Group. Chemical Agents and Related Occupations. *IARC Monogr Eval Carcinog Risks Hum* 2012; 100F:9-562.
13. Vineis P, Wild CP. Global cancer patterns: Causes and prevention. *Lancet* 2014; 383(9916):549–557.
14. Vimala G. Effectiveness of counseling on depression among cancer patients. *J Krishna Inst Med Sci Univ* 2013; 1(2):133–136.
15. Pace TW, Heim CM. A short review on the psychoneuroimmunology of posttraumatic stress disorder: From risk factors to medical comorbidities. *Brain Behav Immun* 2011; 25(1):6–13.
16. Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. *Nat Rev Immunol* 2019; 19(7):433–447.
17. Chen WC, Liu YB, Liu WF, Zhou YY, He HF, Lin S. Neuropeptide Y is an immunomodulatory factor: direct and indirect. *Front Immunol* 2020; 11:580378.
18. Wirth JJ, Ross AC. The influence of cadmium on neuropeptide and hormone signaling in metabolism. *Toxicol Sci*. 2006; 93(2):303–309.
19. Muñoz M, Coveñas R. Substance P / Neurokinin-1 receptor system and cancer: biological evidence and therapeutic perspectives. *J Physiol Biochem* 2019; 75(2):125-133.
20. Hong X, Ma J, Zheng S, Zhao G, Fu C. Advances in the research and application of neurokinin-1 receptor antagonists. *J Zhejiang Univ Sci B* 2024; 25(2):91-105.
21. Gurevich VV, Gurevich EV. GPCR signaling regulation: the role of G protein-coupled receptor kinases (GRKs) and arrestins. *Front Pharmacol* 2019; 10:125.
22. Muñoz M, Coveñas R. The neurokinin-1 receptor: A new target in cancer therapy. *Curr Drug Targets* 2011; 12(6):909–921.
23. Qiuyan C, Tesmer JJG. G protein–coupled receptor interactions with arrestins and GPCR kinases: the unresolved issue of signal bias. *J Biol Chem* 2022; 298(9):102279.
24. Haider RS, Matthees ESF, Drube J, Reichel M, Zabel U, Inoue A, *et al*. β-arrestin1 and 2 exhibit distinct phosphorylation-dependent conformations when coupling to the same GPCR in living cells. *Nat Commun* 2022; 13(1):5638.
25. Sofroniew MV. Astrogliosis. *Cold Spring Harb Perspect Biol* 2015; 7(2): a020420.
26. Baral P, Udit S, Chiu IM. Pain and immunity: Implications for host defence. *Nat Rev Immunol*. 2019; 19(7):433–447.
27. Wess J, Oteng AB, Rivera-Gonzalez O, Gurevich EV, Gurevich VV. β-Arrestins: structure, function, physiology, and pharmacological perspectives. *Pharmacol Rev* 2023; 75(5):854–884.

28. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. *Endocr Rev* 2003; 24(4):389-427.
29. Muñoz M, Rosso M, Coveñas R. Targeting NK1 receptors in cancer: Update on clinical trials. *Curr Drug Targets* 2017; 18(13):1525-1530.
30. Orfali R, Alwatban AZ, Orfali RS, Lau L, Chea N, Alotaibi AM, *et al*. Oxidative stress and ion channels in neurodegenerative diseases: implications for therapy. *Front Physiol* 2024; 15:1320086.
31. Muñoz M, Coveñas R. Involvement of substance P and the NK1 receptor in cancer progression. *Peptides* 2013; 48:1–9.
32. Sofroniew Michael V. Astrogliosis. *Cold Spring Harbor Perspect Biol* 2015; 7(2):a020420
33. Keillor JW, Coveñas R, Muñoz M. Substance P and cancer: New therapeutic avenues. *Curr Med Chem* 2022; 29(18):3053–3068.
34. Rameshwar P, Gascon P. SP-NK1 receptor signaling in hematopoiesis and cancer. *Ann N Y Acad Sci* 2000; 917:647–658.
35. Thomas I, Dickens AM, Posti JP, Czeiter E, Duberg D, Sinioja T, *et al*. Serum metabolome associated with severity of acute traumatic brain injury. *Nat Commun* 2022; 13:2545.
36. Wheway J, Herzog H, Mackay F. NPY and Y receptors in immune regulation-New roles revealed by genetic models. *Neuropeptides* 2007; 41(3):145-153.
37. Franco R, Garrigós C, Lillo J, Rivas-Santisteban R. The potential of metabolomics to find proper biomarkers for addressing the neuroprotective efficacy of drugs aimed at delaying Parkinson's and Alzheimer's disease progression. *Cells* 2024; 13(15):1288.
38. Allen AR, Liu Y, Perry G. Neuropeptide Y in cancer biology: Emerging roles and therapeutic perspectives. *Oncotarget* 2021; 12(19):1863–1875.
39. Zukowska Z. Neuropeptide Y: A new mediator linking stress to obesity and cancer? *Peptides* 2005; 26(2):299-304.
40. Delgado M, Ganea D. Vasoactive intestinal peptide: A neuropeptide with pleiotropic immune functions. *Am J Physiol Cell Physiol* 2001; 280(4): C1037–C1050.
41. Pascetta SA, Kirsh SM, Cameron M, Uniacke J. Pharmacological inhibition of neuropeptide Y receptors Y1 and Y5 reduces hypoxic breast cancer migration, proliferation, and signaling. *BMC Cancer* 2023; 23:494.
42. Semreen AM, Alsoud LO, El-Huneidi W, Ahmed M, Bustanji Y, Abu-Gharbieh E, *et al*. Metabolomics analysis revealed significant metabolic changes in brain cancer cells treated with paclitaxel and/or etoposide. *Int J Mol Sci* 2022; 23(22):13940.
43. Miyamoto M, Kamiyama R, Yokoyama M. CGRP expression and angiogenesis in melanoma. *J Dermatol Sci* 2003; 31(3):175-182.
44. Batra R, Krumsiek J, Wang X, Allen M, Blach C, Kastenmüller G, *et al*. Comparative brain metabolomics reveals shared and distinct metabolic alterations in Alzheimer's disease and progressive supranuclear palsy. *Alzheimers Dement* 2024; 20(12): 8294-8307.
45. Koch M, Acharjee A, Ament Z, Schleicher R, Bevers M, Stapleton C, *et al*. Machine learning–driven metabolomic evaluation of cerebrospinal fluid: insights into poor outcomes after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2021; 88(5):1003–1011.
46. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, *et al*. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; 371(3):224–233.
47. Schmid HA. Effects of somatostatin analogs on the endocrine and exocrine pancreas. *Neuroendocrinology* 2008; 88(2):104–110.
48. Paz-Filho G, Mastronardi C, Franco CB, Wang KB, Wong ML, Licinio J. Leptin: Molecular mechanisms, systemic pro-inflammatory effects, and clinical implications. *Arq Bras Endocrinol Metabol* 2012; 56(9):597–607.
49. Nogueiras R, Pfluger P, Tschöp MH, et al. NPY and energy balance: Insights from NPY-deficient mice. *Peptides* 2008; 29(3):449–458.
50. Ben-Shlomo A, Melmed S. Neuroendocrine tumors of the pancreas. *Nat Rev Endocrinol* 2013; 9(5):267–276.
51. Iyengar NM, Hudis CA, Dannenberg AJ. Obesity and cancer: Local and systemic mechanisms. *Annu Rev Med* 2015; 66:297–309
52. Lotinun S, Rojnuckarin P, Leelahavanichkul A. Immune –metabolic–bone axis in cancer: potential links and therapeutic targets. *Front Immunol* 2021; 12:682652.
53. Ramachandran R, McMahon SB. Neurogenic inflammation and its role in migraine. *Semin Immunopathol* 2014; 36(3):301-314.
54. Park J, Morley TS, Kim M. The adipocyte–cancer cell axis in cancer development and therapy. *Nat Rev Cancer* 2022; 22(6):377–392.

55. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 2004; 92(3):347-355.
56. Gotwals P, Cameron S, Cipolletta D, Cremasco V, Crystal A, Hewes B, *et al*. Prospects for combining targeted and conventional cancer therapy with immunotherapy. *Nat Rev Cancer* 2017; 17(5):286-301.
57. Armaiz-Pena GN, Cole SW, Lutgendorf SK, Sood AK. Neuroendocrine influences on cancer progression. *Brain Behav Immun* 2013; 30 Suppl (Suppl): S19–25.
58. Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adipokines in obesity-associated breast cancer: an insight into the molecular mechanisms and therapeutic potential. *Mol Cancer Res* 2013;11(10):1210-23
59. Bajic JE, Johnston IN, Howarth GS. From bacteria to B cells: a role for the gut microbiota in gastrointestinal cancer. *Front Cell Infect Microbiol* 2020; 10:534644.
60. Joshi S, Sankaranarayanan R. Opportunities for cervical cancer prevention in India. *J Krishna Inst Med Sci Univ* 2015; 4(1):8–17.

Author for Correspondence:
Dr. Mike Osagie Odigie, Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Edo State University, Iyamoh, Edo State, Nigeria Email: odigie.mike@edouniversity.edu.ng, Tel: +2347036844454

How to cite this article:
Odigie MO, Osagie LOO, Gbagbeke KO, Dawus TT. The neuroimmune–metabolic triad in cancer: Mechanistic links, carcinogen–neuropeptide interactions, and translational therapeutic insights. *J Krishna Inst Med Sci Univ* 2025; 14(3):18-37

Submitted: *18-Mar-2025* ***Accepted:*** *28-May-2025* ***Published:*** *01-July-2025*