

RESEARCH MONOGRAPH . COMPOUND PROFILE

Spexin

A 14-amino-acid C-terminally amidated neuropeptide of the galanin/kisspeptin/spexin superfamily, identified by bioinformatic hidden Markov model screening of the human proteome in 2007 and subsequently characterized as a satiety factor, metabolic regulator, anxiolytic peptide, and antinociceptive agent operating through selective activation of galanin receptor subtypes 2 and 3.

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ABSTRACT

Spexin (SPX), also designated neuropeptide Q (NPQ), is a 14-amino-acid peptide hormone encoded by the C12orf39 gene on human chromosome 12 and processed from a 116-amino-acid prepropeptide by dibasic cleavage and C-terminal alpha-amidation [1, 2]. The mature human sequence (NWTPQAMLYLKGAQ-NH₂) is perfectly conserved across all mammalian species examined and differs by only one to two residues from teleost orthologs, placing spexin among the most evolutionarily conserved vertebrate peptide hormones [3]. First identified in 2007 by Mirabeau and colleagues through a hidden Markov model algorithm designed to detect novel secreted peptide hormones in the human genome, and first confirmed biochemically in murine esophageal and gastric tissue [1], spexin was subsequently shown to activate galanin receptor type 2 (GALR2) and galanin receptor type 3 (GALR3) with nanomolar potency (EC₅₀ values of approximately 45.7 and 112.2 nM respectively) while showing no measurable activity at galanin receptor type 1 (GALR1) [4, 5]. This receptor selectivity profile distinguishes spexin from galanin itself, which activates all three galanin receptor subtypes, and establishes spexin as a naturally occurring GALR2/GALR3-selective agonist. The peptide is expressed broadly across central and peripheral tissues including the hypothalamus, hippocampus, amygdala, adipose tissue, liver, gastrointestinal tract, pancreas, kidney, heart, ovary, and testis [6, 7]. Functionally, spexin has been characterized as a satiety factor that suppresses food intake in goldfish, zebrafish, and mice through hypothalamic regulation of orexigenic (neuropeptide Y, agouti-related protein) and anorexigenic (proopiomelanocortin,

cocaine- and amphetamine-regulated transcript) neuropeptides [8, 9, 10]. In adipose tissue, spexin inhibits long-chain fatty acid uptake into adipocytes and promotes weight loss in diet-induced obese rodents [11]. Circulating spexin concentrations are significantly reduced in human obesity, type 1 diabetes, type 2 diabetes, metabolic syndrome, and polycystic ovary syndrome, establishing the peptide as a candidate biomarker for metabolic dysregulation [12, 13, 14]. Beyond metabolic regulation, spexin-based GALR2-selective agonists produce anxiolytic effects in murine behavioral models [5], and the metabolically stabilized analog LIT-01-144 produces potent non-opioid peripheral antinociception in persistent inflammatory pain through GALR2 activation [15]. In reproductive physiology, spexin inhibits gonadotropin (LH and FSH) synthesis and secretion in multiple vertebrate species and negatively regulates ovarian steroidogenesis [16, 17]. No human clinical trials of exogenous spexin administration have been reported; the compound remains in the preclinical and biomarker research phase. This monograph reviews the chemistry, gene structure, and peptide processing of spexin; the receptor pharmacology and signal transduction through GALR2 and GALR3; the preclinical pharmacology across metabolic, appetite, nociceptive, anxiolytic, reproductive, and cardiovascular domains; the human biomarker and associative clinical evidence; sourcing and handling considerations for research-grade material; analog development for metabolic stability; and a comparative assessment against five related peptide or receptor-targeted candidates on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Recommended name: Spexin (SPX).

Alternative names: Neuropeptide Q (NPQ); C12orf39 peptide; spexin hormone.

Gene name: C12orf39 (human); also annotated as SPX in HUGO nomenclature and OMIM entry 619246 [2].

Chemical Abstracts Service registry number: 1370290-58-6 (free base, synthetic peptide corresponding to the mature human/rat sequence) [18].

UniProt accession: Q9BT56 (Homo sapiens spexin hormone precursor) [2].

Sequence (mature peptide, human): H-Asn-Trp-Thr-Pro-Gln-Ala-Met-Leu-Tyr-Leu-Lys-Gly-Ala-Gln-NH₂ (single-letter code: NWTPQAMLYLKGAQ-NH₂). The C-terminal glutamine is alpha-amidated, a post-translational modification essential for full biological activity [1, 3].

IUPAC peptide name: L-asparaginyl-L-tryptophyl-L-threonyl-L-prolyl-L-glutamyl-L-alanyl-L-methionyl-L-leucyl-L-tyrosyl-L-leucyl-L-lysyl-glycyl-L-alanyl-L-glutaminamide.

1.2 Structural class and chemistry

Spexin belongs to the galanin/kisspeptin/spexin superfamily of neuropeptides, a group sharing a common ancestral gene that diverged early in vertebrate evolution [19]. The three peptide families (galanin, kisspeptin, spexin) share structural features including C-terminal amidation, intermediate peptide length (14 to 30 residues), and signaling through rhodopsin-family G-protein-coupled receptors of the galanin receptor subfamily.

Molecular formula: C₆₈H₁₀₃N₁₇O₁₈S (free base, amidated form).

Molecular weight: Approximately 1,547.7 Da (monoisotopic mass approximately 1,545.74 Da) [18].

Physical properties: White to off-white lyophilized powder when supplied as synthetic material. Freely soluble in water (as the trifluoroacetate or acetate salt); soluble in dimethyl sulfoxide; sparingly soluble in apolar organic solvents. The tryptophan residue at position 2 confers ultraviolet absorbance at 280 nm suitable for spectrophotometric quantification.

Disulfide bonds: None. The peptide contains no cysteine residues.

Post-translational modifications: The sole characterized post-translational modification of the mature peptide is C-terminal alpha-amidation at Gln14, catalyzed by peptidylglycine alpha-amidating monooxygenase acting on the Gly-Arg-Arg processing signal in the prepropeptide [1, 3].

1.3 Gene structure and peptide processing

The human spexin gene (C12orf39) is located on chromosome 12 and encodes a 116-amino-acid prepropeptide [2]. The prepropeptide contains an N-terminal hydrophobic signal peptide directing secretory pathway entry, followed by a propeptide segment, the mature 14-amino-acid spexin sequence flanked by dibasic cleavage sites (Lys-Arg at the N-terminal flank and Gly-Arg-Arg at the C-terminal flank), and a C-terminal extension [1, 3]. Processing in the endoplasmic reticulum and Golgi apparatus involves signal peptide removal, prohormone convertase cleavage at the dibasic sites, carboxypeptidase E removal of the C-terminal basic residues, and peptidylglycine alpha-amidating monooxygenase conversion of the exposed glycine to the C-terminal amide [3]. The processed, amidated 14-mer is the biologically active form secreted into the circulation and the extracellular space.

In non-mammalian vertebrates, genome duplication events have produced paralogous spexin genes (spx1 and spx2 in teleosts), with spx1 more closely resembling the mammalian ortholog and spx2 showing greater sequence divergence [3].

1.4 Solution structure

The NMR solution structure of mouse spexin (identical in sequence to human spexin) was determined by Wong et al. (2021) in 60 percent trifluoroethanol/water solvent [20]. The structure reveals a C-terminal alpha-helix spanning approximately residues 5 through 14, with the N-terminal tetrapeptide (Asn1-Trp2-Thr3-Pro4) adopting a more extended or flexible conformation. Far-UV circular dichroism spectroscopy confirmed approximately 75 percent helical content under structure-

promoting conditions. Molecular docking and dynamics simulations demonstrated that the C-terminal alpha-helix inserts into the transmembrane binding pocket of GALR2 and GALR3, with key interactions involving Asn1, Leu8, and Leu10 contacting residues in extracellular loops 1 and 2 and transmembrane domains 2 and 7 of the receptors [20].

2. Abstract

Spexin (SPX/NPQ) is a 14-amino-acid, C-terminally amidated neuropeptide of the galanin superfamily that functions as an endogenous selective agonist of galanin receptor type 2 (GALR2, EC50 approximately 45.7 nM) and galanin receptor type 3 (GALR3, EC50 approximately 112.2 nM) without measurable activity at galanin receptor type 1 (GALR1) [4, 5]. Identified by bioinformatic screening of the human genome in 2007 [1] and functionally characterized as a satiety factor in goldfish by Wong et al. (2013) [8], spexin has since been established as a pleiotropic regulator of energy homeostasis, appetite, lipid metabolism, nociception, anxiety, reproduction, gastrointestinal motility, and cardiovascular function across vertebrate species [6, 7, 19].

The metabolic regulatory profile is the most extensively characterized axis of spexin biology. Intracerebroventricular and intraperitoneal administration of spexin suppresses food intake in goldfish, zebrafish, and mice through downregulation of hypothalamic neuropeptide Y (NPY) and agouti-related protein (AgRP) and upregulation of proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) [8, 9, 10]. Spexin gene knockout in zebrafish produces hyperphagia with elevated *agrp1* expression [9]. In peripheral tissues, spexin inhibits long-chain fatty acid uptake into adipocytes through a GALR2-dependent mechanism and reduces body weight in diet-induced obese mice [11]. A 2024 study demonstrated that spexin promotes white adipose tissue browning through the JAK2-STAT3 signaling pathway, ameliorating obesity-related metabolic disorders [21].

Circulating spexin concentrations are significantly reduced in human subjects with obesity, type 2 diabetes, type 1 diabetes, metabolic syndrome, and polycystic ovary syndrome compared to healthy controls [12, 13, 14, 22]. The inverse correlation between spexin levels and body mass index, fasting glucose, insulin resistance (HOMA-IR), and triglyceride concentrations has been replicated across multiple populations and establishes spexin as a candidate circulating biomarker for metabolic health status [12, 13].

Beyond metabolism, spexin-based GALR2-selective agonists (produced by quadruple amino acid substitution in the spexin backbone) exhibit anxiolytic activity in murine elevated plus maze and open field tests [5]. The metabolically stabilized analog LIT-01-144, bearing an N-terminal fluorocarbon chain modification, produces potent non-opioid peripheral antinociception in a mouse model of persistent inflammatory pain through GALR2 activation, with no requirement for opioid receptor engagement [15]. In reproductive endocrinology, spexin inhibits gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone synthesis and secretion in fish, birds, and some mammals, and negatively regulates ovarian granulosa cell steroidogenesis [16, 17]. The peptide also enhances bowel motility through GALR2-mediated activation of L-type voltage-dependent calcium channels in intestinal smooth muscle [23].

No human interventional clinical trials of exogenous spexin have been reported. The compound remains in the preclinical pharmacology and biomarker association phase. Analog development programs have produced GALR2-selective and metabolically stabilized variants with improved serum half-life and receptor subtype selectivity [5, 15, 24]. The research trajectory positions spexin and its analogs as candidates for therapeutic development in obesity, type 2 diabetes, non-opioid analgesia, and anxiety disorders.

3. Discovery and Development History

3.1 Bioinformatic identification

Spexin was identified in 2007 by Mirabeau, Perlas, Bhatt, and colleagues at the European Molecular Biology Laboratory (EMBL) through a computational hidden Markov model (HMM) algorithm designed to detect novel peptide hormones in sequenced vertebrate genomes [1]. The algorithm integrated sequence features characteristic of secreted peptide hormones, including signal peptide presence, dibasic cleavage sites, C-terminal amidation signals, and short mature peptide length. Application of the algorithm to the human genome identified C12orf39 as encoding a candidate peptide hormone. Biochemical confirmation was achieved by immunohistochemical detection of the mature peptide in murine esophageal and gastric tissue [1]. The name "spexin" was coined by the discoverers; the alternative name "neuropeptide Q" (NPQ) was applied contemporaneously based on the initial assumption of exclusive neural expression, which subsequent studies disproved [6].

3.2 Functional characterization as a satiety factor

The first functional characterization of spexin was published by Wong et al. (2013) in goldfish [8]. Intracerebroventricular injection of synthetic spexin inhibited both basal and NPY-stimulated food consumption in a dose-dependent manner. The effect was accompanied by decreased expression of orexigenic factors (NPY, AgRP) and increased expression of anorexigenic factors (POMC, CCK, CART) in brain areas involved in appetite control. Postprandial spexin mRNA levels increased in the goldfish brain, consistent with a physiological satiety signal inducible by food intake [8]. This study established the functional paradigm for spexin research and identified the hypothalamic appetite-regulatory circuit as the primary central target.

3.3 Receptor deorphanization

The receptor pharmacology of spexin was elucidated by Kim et al. (2014) through systematic screening of the peptide against a panel of G-protein-coupled receptors [4]. Spexin activated GALR2 and GALR3 in calcium mobilization and cAMP inhibi-

tion assays but showed no measurable agonism at GALR1 or at other tested receptors. The EC50 values were approximately 45.7 nM at human GALR2 and approximately 112.2 nM at human GALR3 [4]. This finding placed spexin within the galanin receptor ligand family and explained its functional overlap with galanin in appetite regulation while establishing the GALR2/GALR3 selectivity that distinguishes it from the broad-spectrum galanin peptide.

3.4 Metabolic biomarker studies in humans

Beginning in 2014, multiple clinical biomarker studies established that circulating spexin concentrations are significantly lower in obese adults compared to normal-weight controls. Al-Daghri et al. (2018) reported that spexin levels are inversely associated with metabolic syndrome components in a Saudi Arabian cohort [12]. Karber et al. (2018) demonstrated significantly decreased serum spexin in patients with type 1 and type 2 diabetes compared to healthy controls [13]. A 2021 systematic review by Behrendt et al. confirmed the consistency of reduced spexin in obesity across 14 published studies from multiple populations [14]. These findings positioned spexin as a candidate biomarker and potential therapeutic agent for metabolic disease.

3.5 Analog development

Reyes-Alcaraz et al. (2016) reported the development of spexin-based GALR2-specific agonists by systematic amino acid substitution [5]. The key substitutions (Gln5-Asn, Met7-Ala, Lys11-Phe, Ala13-Pro) abolished GALR3 activity while preserving GALR2 potency. Addition of D-Asn at position 1 improved serum stability. The resulting compound (dN1-Qu) produced anxiolytic effects upon intracerebroventricular administration in mice [5]. In 2026, Gaveriaux-Ruff and colleagues reported LIT-01-144, a metabolically resistant spexin analog with an N-terminal fluorocarbon chain, demonstrating potent non-opioid peripheral antinociception through GALR2 in persistent inflammatory pain models [15].

3.6 Current development status

No investigational new drug application or clinical trial of exogenous spexin or spexin analogs has been reported as of the monograph revision date. The compound is in the preclinical pharmacology, structure-activity relationship optimiza-

tion, and biomarker validation phase. Patent applications for metabolically stable spexin analogs have been filed (EP3257864A1, EP3472195B1), covering pharmaceutical compositions for the treatment of metabolic disorders and pain [24].

4. Mechanism of Action

4.1 Galanin receptor type 2 (GALR2) activation

GALR2 is a seven-transmembrane G-protein-coupled receptor coupled primarily to Gq/11 signaling, with activation producing phospholipase C (PLC) hydrolysis of phosphatidylinositol 4,5-bisphosphate, generation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG), mobilization of intracellular calcium from endoplasmic reticulum stores, and activation of protein kinase C [25, 26]. GALR2 is expressed in the hypothalamus (arcuate nucleus, paraventricular nucleus, ventromedial hypothalamus), hippocampus, amygdala, dorsal root ganglia, gastrointestinal smooth muscle, adipose tissue, and ovary [25].

Spexin binding to GALR2 produces the following characterized downstream effects:

In the hypothalamus: suppression of NPY and AgRP expression in the arcuate nucleus, activation of POMC neurons, and consequent reduction of food intake [10]. The mechanism involves phosphorylation of calcium/calmodulin-dependent protein kinase II (p-CaMKII) and induction of c-Fos in hypothalamic feeding centers [10].

In adipose tissue: inhibition of fatty acid transport protein-mediated long-chain fatty acid uptake into adipocytes [11]. The GALR2 dependence was confirmed by GALR2 antagonist blockade experiments.

In intestinal smooth muscle: activation of L-type voltage-dependent calcium channels (Cav1.2), producing increased intracellular calcium and enhanced contractility [23]. This mechanism increases bowel motility and was confirmed by L-type channel blockade with nifedipine.

In dorsal root ganglia: modulation of nociceptive neuron excitability, producing peripheral antinociception in inflammatory pain states through the GALR2-dependent mechanism characterized for LIT-01-144 [15].

In the amygdala and hippocampus: anxiolytic and antidepressant-like effects, potentially mediated by modulation of serotonergic and GABAergic circuits [5, 27].

4.2 Galanin receptor type 3 (GALR3) activation

GALR3 is coupled primarily to inhibitory Gi/o proteins, with activation producing inhibition of adenylyl cyclase, reduction of intracellular cyclic AMP, activation of G-protein-coupled inwardly rectifying potassium channels (GIRK), and inhibition of voltage-gated calcium channels [25, 26]. GALR3 is expressed at lower density than GALR2 in most tissues but is present in the hypothalamus, hippocampus, pituitary gland, and peripheral tissues.

Spexin activation of GALR3 contributes to:

Appetite suppression: GALR3-mediated inhibition of NPY neurons in the hypothalamus [10]. Peripheral spexin administration in mice produces anorectic effects partially mediated by GALR3 signaling.

Reproductive axis inhibition: GALR3 activation in the pituitary contributes to suppression of gonadotropin release [16].

The relative contributions of GALR2 and GALR3 to individual physiological effects are being delineated through subtype-selective agonists and antagonists [5].

4.3 Absence of GALR1 activity

Spexin shows no measurable agonist activity at GALR1 at concentrations up to 10 micromolar in heterologous expression systems [4]. This selectivity distinguishes spexin from galanin (which activates GALR1 with high affinity) and is structurally determined by residues in the spexin N-terminus and mid-sequence that differ critically from the corresponding galanin positions required for GALR1 binding [20]. The GALR1-sparing profile may explain the absence of the sedative and memory-impairing effects associated with GALR1 activation by galanin.

4.4 Downstream metabolic signaling pathways

In adipose tissue, spexin activates the JAK2-STAT3 signaling pathway to promote browning of white adipose tissue, increasing expression of uncoupling protein 1 (UCP1) and other thermogenic markers [21]. This mechanism converts energy-storing white adipocytes toward energy-dissipating beige/brown adipocytes and represents a distinct metabolic pathway from the acute fatty acid uptake inhibition.

In skeletal muscle, spexin increases glucose uptake through upregulation of glucose transporter type 4 (GLUT4) translocation to the plasma membrane [28]. The signaling pathway involves GALR2-mediated activation of AMPK (5' AMP-activated protein kinase).

In hepatocytes, spexin modulates lipogenesis by suppressing expression of sterol regulatory element-binding protein 1c (SREBP-1c) and fatty acid synthase (FAS), while promoting beta-oxidation through upregulation of carnitine palmitoyl-transferase 1A (CPT1A) [28].

4.5 Leptin interaction

Spexin expression in the hypothalamus is positively regulated by leptin signaling [29]. Leptin administration upregulates spexin mRNA in the arcuate nucleus, and spexin mediates a portion of leptin's anorectic effect through GALR2/GALR3-dependent suppression of food intake. In leptin-deficient (ob/ob) and leptin-resistant (db/db) mice, hypothalamic spexin expression is reduced, suggesting that spexin deficiency contributes to the hyperphagia of leptin-resistant obesity [29].

5. Pharmacokinetics

5.1 Endogenous circulating levels

Circulating spexin concentrations in healthy lean human adults have been reported in the range of 0.5 to 2.5 ng/mL (approximately 0.3 to 1.6 nM) by enzyme-linked immunosorbent assay [12, 13]. Levels are significantly lower (by 30 to 60 percent) in obese subjects, in patients with type 2 diabetes, and in patients with metabolic syndrome [12, 13, 14]. Spexin levels correlate inversely with body mass index, waist circumference, fasting glucose, fasting insulin, HOMA-IR, and serum triglycerides, and correlate positively with high-density lipoprotein cholesterol [12].

Postprandial spexin levels increase in animal models, consistent with a meal-induced satiety signal. The gastric glandular epithelium is a principal peripheral source, with spexin mRNA and peptide content increasing after food intake in mice [10].

5.2 Absorption and distribution of exogenous spexin

Exogenous synthetic spexin administered by intraperitoneal injection in rodents produces measurable increases in plasma concentration within minutes. The peptide distributes widely, consistent with its small molecular weight and hydrophilic character. Central nervous system penetration after peripheral administration has been demonstrated functionally (appetite suppression, anxiolysis) but quantitative blood-brain barrier permeability coefficients have not been published for native spexin [10].

Intracerebroventricular administration bypasses the blood-brain barrier and produces direct central effects at doses approximately 10-fold lower than peripheral doses [8, 10].

5.3 Metabolism and half-life

As a small unmodified peptide, native spexin is subject to rapid proteolytic degradation in serum. The serum half-life of unmodified synthetic spexin has not been precisely reported in a formal pharmacokinetic study but is estimated at minutes to

tens of minutes based on general peptide stability principles and the rapid development of stabilized analogs [5, 15]. The methionine at position 7 is susceptible to oxidation, and multiple peptide bonds are accessible to serum proteases including dipeptidyl peptidase IV and neutral endopeptidase.

The metabolically stabilized analog dN1-Qu (D-Asn1 substitution plus quadruple mutation) shows improved serum stability relative to native spexin [5]. LIT-01-144, bearing an N-terminal fluorocarbon chain, demonstrates significantly prolonged plasma residence time and no central nervous system penetration, enabling selective peripheral GALR2 activation [15].

5.4 Elimination

Renal filtration is expected to be the principal elimination pathway for circulating spexin given the molecular weight (approximately 1,548 Da) below the glomerular filtration threshold. Proteolytic fragments are presumably cleared by renal and hepatic mechanisms. Formal radiolabeled elimination studies have not been published.

5.5 Routes of administration in research

Research applications have employed: intracerebroventricular injection (goldfish, mice; 0.1 to 10 nmol; for central feeding and behavioral effects) [8, 10]; intraperitoneal injection (mice, rats; 35 to 70 micrograms per kilogram; for peripheral metabolic and appetite effects) [10, 11]; and in vitro application (nanomolar to low-micromolar concentrations in cell culture for receptor pharmacology and adipocyte studies) [4, 11]. Oral bioavailability of the native peptide is expected to be negligible owing to gastrointestinal proteolysis; no oral administration studies have been published.

6. Preclinical Pharmacology

6.1 Appetite and food intake

The satiety function of spexin is the most extensively characterized preclinical effect. Key findings include:

Wong et al. (2013): Intracerebroventricular spexin in goldfish inhibited basal food consumption by approximately 30 to 50 percent and NPY-stimulated food consumption by approximately 40 to 60 percent in a dose-dependent manner [8]. Effect was accompanied by decreased NPY and AgRP mRNA and increased POMC, CCK, and CART mRNA in brain feeding centers.

Kolodziejski et al. (2018): Zebrafish spexin gene (*spx1*) knockout produced significant hyperphagia with elevated *agrp1* expression compared to wild-type fish [9]. Rescue by exogenous spexin administration confirmed the gene-phenotype relationship.

Lv et al. (2020): Peripheral (intraperitoneal) spexin injection inhibited food intake in C57BL/6 mice at 35 micrograms per kilogram body weight [10]. The anorectic effect was mediated by GALR3 and involved inhibition of NPY via phosphorylated CaMKII and c-Fos induction in the hypothalamic arcuate nucleus.

Wong et al. (2021): Intracerebroventricular spexin in mice functioned as a satiety factor through regulatory actions within the hypothalamus, with effects on AgRP, NPY, POMC, and CART expression in the arcuate nucleus and ventromedial hypothalamus [30].

6.2 Obesity and lipid metabolism

Walewski et al. (2014): Spexin reduced adipocyte uptake of long-chain fatty acids and produced weight loss in rodents with diet-induced obesity [11]. The effect was GALR2-dependent and was associated with reduced adipocyte expression of fatty acid transport proteins. Chronic spexin administration (intraperitoneal, 14 days) reduced body weight, adipose mass, and plasma triglycerides in high-fat-diet-fed mice.

Li et al. (2024): Spexin ameliorated obesity-related metabolic disorders in high-fat-diet mice through promoting white adipose tissue browning mediated by the JAK2-STAT3 pathway [21]. After 12 weeks of treatment, spexin significantly decreased body weight, reduced serum lipid levels, and improved insulin sensitivity. UCP1 expression was markedly upregulated in subcutaneous and visceral white adipose depots.

6.3 Glucose metabolism and diabetes

In skeletal muscle, spexin promotes GLUT4 translocation and glucose uptake through AMPK activation [28]. In pancreatic islets, spexin modulates insulin secretion, though the direction of effect (stimulatory versus inhibitory) varies with experimental conditions and glucose concentration [28]. A spexin-based GALR2 agonist improved renal injury in mice with streptozotocin-induced type 2 diabetes, attenuating renal fibrosis through suppression of TGF-beta/Smad signaling [31].

6.4 Nociception and analgesia

Toll et al. (2017): Spexin and progesterone synergistically attenuated pain sensitivity in ovariectomized rats, suggesting a hormonal interaction relevant to sex-specific pain conditions [32].

Gaveriaux-Ruff et al. (2026): The metabolically resistant spexin analog LIT-01-144 produced potent non-opioid peripheral antinociception in a complete Freund's adjuvant (CFA) model of persistent inflammatory pain in mice [15]. Antinociception was mediated specifically by peripheral GALR2 activation and was independent of opioid, NSAID, and cannabinoid receptor mechanisms. The compound showed no antinociceptive effect in naive animals, suggesting selectivity for pathological pain states. The effect was blocked by a GALR2 antagonist (M871) and absent in GALR2 knockout animals [15].

6.5 Anxiety and mood

Reyes-Alcaraz et al. (2016): The GALR2-selective spexin analog dN1-Qu produced anxiolytic effects in the elevated plus maze and open field test in mice upon intracerebroventricular administration [5]. Effect magnitude was comparable to diazepam at the tested dose.

Overexpression of spexin in the dorsal habenula of zebrafish reduced anxiety-like behavior in a novel tank test, supporting a conserved anxiolytic role across vertebrates [27].

Ma et al. (2019): A spexin-based GALR2 agonist was proposed for comorbid mood disorders and abnormal body weight, addressing the clinical overlap between obesity and anxiety/depression through a single pharmacological target [33].

6.6 Gastrointestinal motility

Lin et al. (2015): Spexin enhanced bowel movement in mice through GALR2-mediated activation of L-type voltage-dependent calcium channels in intestinal smooth muscle [23]. The prokinetic effect was blocked by nifedipine and by GALR2 antagonism, establishing the signaling pathway.

6.7 Reproductive axis

Spexin inhibits gonadotropin synthesis and secretion across multiple vertebrate species. In tilapia, both spexin paralogs inhibit FSH and LH through a specific galanin receptor (Galr2b) [16]. In mammals, spexin negatively impacts steroidogenesis and proliferation in human granulosa cells, with potential relevance to polycystic ovary syndrome pathophysiology [17]. Plasma spexin levels are significantly lower in women with PCOS compared to healthy controls [22].

6.8 Cardiovascular function

Emerging evidence links spexin to cardiovascular homeostasis. Spexin protects cardiomyocytes from hypoxia-induced metabolic and mitochondrial dysfunction [34]. Spexin expression is altered in cardiac tissue following ischemia-reperfusion injury, and exogenous administration has shown cardioprotective effects in some models, though exogenous spexin has also been reported to aggravate renal ischemia-reperfusion injury in one study, indicating that the dose-response and tissue-specific effects require further characterization [35].

7. Clinical Evidence Base

7.1 Human biomarker associations

The clinical evidence for spexin in humans is entirely observational and associative; no interventional trials of exogenous spexin have been conducted. The principal clinical findings are:

Obesity: Multiple studies across diverse populations (Saudi Arabian, Egyptian, Turkish, Indian, European) report significantly lower circulating spexin in obese subjects compared to lean controls [12, 13, 14]. The Al-Daghri et al. (2018) study in 365 Saudi Arabian adults found spexin levels inversely associated with BMI, waist circumference, fasting glucose, fasting insulin, HOMA-IR, triglycerides, and positively associated with HDL cholesterol [12]. Effect sizes range from 30 to 60 percent reduction in circulating spexin in obese versus lean groups.

Type 2 diabetes mellitus: Karber et al. (2018) reported significantly decreased serum spexin in 56 type 2 diabetes patients compared to 56 age- and sex-matched controls [13]. The reduction persisted after adjustment for BMI, suggesting an independent diabetes-related deficit beyond the obesity contribution. Subsequent studies in Indian and Egyptian populations replicated this finding [36, 37].

Type 1 diabetes mellitus: Karber et al. (2018) also found reduced spexin in type 1 diabetes patients, indicating the deficit is not specific to insulin-resistant metabolic disease [13].

Metabolic syndrome: Spexin levels correlate with the number of metabolic syndrome components present, with the lowest levels observed in subjects meeting full diagnostic criteria [12].

Polycystic ovary syndrome: Circulating spexin is reduced in PCOS, with an area under the ROC curve of 0.757 for distinguishing PCOS from healthy controls [22].

Bariatric surgery: Short-term changes in plasma spexin following laparoscopic sleeve gastrectomy have been characterized, with correlations to simultaneous changes in kisspeptin and galanin levels [38].

Exercise: Kumar et al. (2020) reported that structured exercise programs increase circulating spexin in obese and diabetic subjects, correlating with improvements in metabolic parameters and suggesting that exercise-induced spexin elevation mediates some of the metabolic benefits of physical activity [39].

7.2 Absence of interventional trials

No human clinical trial administering exogenous spexin or spexin analogs has been registered or reported. The barriers to clinical translation include: (a) the short serum half-life of native spexin requiring parenteral administration and frequent dosing; (b) the absence of formal toxicology packages suitable for investigational new drug applications; (c) the pleiotropic receptor pharmacology (GALR2 and GALR3 activation with diverse tissue effects) that complicates therapeutic index estimation; and (d) the absence of oral bioavailability for the native peptide. Development of metabolically stabilized, subtype-selective analogs (dN1-Qu, LIT-01-144) is intended to address these barriers [5, 15, 24].

7.3 Clinical development trajectory

The clinical positioning of spexin is pre-investigational. The most advanced analog programs (LIT-01-144 for non-opioid analgesia; spexin-based GALR2 agonists for metabolic disease) are in late preclinical development with patent protection [15, 24, 31]. The biomarker evidence supports spexin deficiency as a feature of metabolic disease, but causality (whether reduced spexin drives disease or results from disease) has not been established by interventional evidence.

8. Sourcing and Quality Verification

8.1 Commercial sources

Synthetic spexin (corresponding to the mature human/rat 14-amino-acid amidated peptide) is available from multiple peptide and chemical suppliers at research grade (greater than 95 percent purity by HPLC):

Tocris Bioscience (catalog number 6090), Sigma-Aldrich/Merck, Cayman Chemical, Alomone Labs (catalog SPS-100), AbMole BioScience, Phoenix Pharmaceuticals, MedChemExpress, Isca Biochemicals, and others [18]. Material is supplied as the trifluoroacetate (TFA) salt or acetate salt, typically in 0.1 mg to 1 mg quantities, with pricing in the range of \$150 to \$500 per milligram depending on quantity and supplier.

Custom synthesis at larger scale (multi-milligram to gram) is available from contract peptide manufacturers employing solid-phase Fmoc chemistry.

8.2 Quality verification

Investigators should confirm compound identity and purity on every lot through:

- Reversed-phase high-performance liquid chromatography (RP-HPLC) area-percent purity, target greater than 95 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ approximately 1548.7 for the amidated form)
- Amino acid analysis to confirm composition
- Confirmation of C-terminal amidation (mass spectrometry or specific enzymatic assay), as the non-amidated form has reduced biological activity
- Peptide content determination (correcting for counterion, moisture, and salt content), as lyophilized peptide preparations often contain 50 to 80 percent peptide by weight

8.3 Pharmaceutical grade

No pharmaceutical-grade spexin preparation exists, as the compound is not an approved medicine in any jurisdiction. All available material is research grade. Investigators using spexin for in vivo studies should verify endotoxin levels by Limulus amebocyte lysate assay if parenteral administration is planned.

9. Reconstitution and Handling

9.1 Reconstitution

Spexin (as the TFA or acetate salt) is supplied as a white lyophilized powder. Recommended reconstitution protocols:

For in vitro studies: Reconstitute in sterile water or phosphate-buffered saline (PBS, pH 7.4) at 0.1 to 1 mg/mL to prepare a stock solution. The peptide is freely soluble in aqueous buffers at these concentrations. For higher concentrations or for poor-solubility lots, brief sonication (30 seconds in a bath sonicator) may assist dissolution. DMSO may be used as an alternative primary solvent at up to 10 mg/mL, with subsequent dilution into aqueous buffer for cell treatment (final DMSO concentration should not exceed 0.1 percent for cell-based assays).

For in vivo studies: Reconstitute in sterile normal saline (0.9 percent NaCl) or artificial cerebrospinal fluid for intracerebroventricular injection. Filter-sterilize through 0.22-micrometer syringe filter if endotoxin-tested water is not available. Prepare fresh daily or aliquot and freeze.

9.2 Storage

Lyophilized powder: Store at minus 20 degrees Celsius, desiccated. Stable for at least 2 years under these conditions.

Reconstituted solution: Store aliquots at minus 20 or minus 80 degrees Celsius. Avoid repeated freeze-thaw cycles (limit to 3 or fewer). Working aliquots may be stored at 2 to 8 degrees Celsius for up to 7 days.

Methionine oxidation: The methionine residue at position 7 is susceptible to oxidation. Long-term storage of aqueous solutions should include degassing with nitrogen or argon. Oxidized spexin (methionine sulfoxide at position 7) may have reduced receptor binding; investigators should monitor for oxidation by mass spectrometry if storing solutions for extended periods.

9.3 Handling considerations

The peptide is non-hazardous at research quantities but should be handled with standard laboratory precautions for bioactive peptides. Gloves and eye protection are recommended. Given the appetite-suppressing and metabolic-regulatory activities, inadvertent self-administration (though highly unlikely at research quantities) should be avoided through standard injection safety practices.

The tryptophan residue at position 2 confers fluorescence (excitation approximately 280 nm, emission approximately 340 nm) that can be used for qualitative identity confirmation and for monitoring peptide in solution.

10. Stack Interactions and Combinations

10.1 Interactions with galanin receptor ligands

Galanin: Spexin and galanin share GALR2 and GALR3 as targets. Concurrent administration would produce additive or competitive effects at these receptors depending on relative concentrations and affinities. Galanin additionally activates GALR1, producing effects (sedation, memory impairment) that spexin does not.

Galanin-like peptide (GALP): GALP preferentially activates GALR2 and also interacts with the galanin family system. Combination with spexin at GALR2 is pharmacologically redundant.

GALR2 antagonists (M871): Block the effects of spexin at GALR2 and are used experimentally to dissect GALR2-mediated from GALR3-mediated effects.

10.2 Interactions with appetite-regulatory peptides

Neuropeptide Y (NPY): Spexin opposes NPY signaling in the hypothalamus. Combination would predict attenuation of NPY-driven food intake, as demonstrated experimentally [8].

Leptin: Spexin mediates a portion of leptin's anorectic effect. In leptin-deficient states, spexin supplementation may partially restore appetite suppression [29].

GLP-1 receptor agonists (semaglutide, liraglutide): Spexin and GLP-1 agonists suppress appetite through distinct receptor mechanisms (GALR2/GALR3 versus GLP-1R). Combination has not been tested but would theoretically produce additive anorexia.

10.3 Metabolic drug interactions

Metformin: Both metformin and spexin activate AMPK in skeletal muscle and liver. Combination effects on glucose uptake have not been characterized but additive benefit is plausible.

Insulin: Spexin modulates insulin secretion and insulin sensitivity. No characterized antagonistic interaction; additive improvement in glucose homeostasis is expected.

Statins: No known interaction. Spexin's effects on lipid metabolism operate through fatty acid uptake and oxidation rather than cholesterol biosynthesis.

10.4 Analgesic combinations

Opioids: LIT-01-144 (spexin analog) produces antinociception independent of opioid receptors [15]. Combination with opioids has not been studied but the independent mechanisms suggest potential for opioid-sparing synergy.

NSAIDs: No known pharmacokinetic or pharmacodynamic interaction. The mechanisms are independent.

10.5 Reproductive hormone interactions

GnRH agonists/antagonists: Spexin suppresses gonadotropins; concurrent GnRH analogs would produce additive reproductive axis suppression.

Combined oral contraceptives: No characterized interaction; theoretical additive gonadotropin suppression.

11. Adverse Events and Safety Signal

11.1 Preclinical safety observations

No formal toxicology study of spexin has been published. The available safety information derives from efficacy studies in which adverse observations were incidentally reported:

Acute administration (mice, rats, goldfish): No mortality, seizure activity, sedation, or visible distress has been reported at doses producing maximum pharmacological effect (up to 70 micrograms/kg IP in mice, up to 10 nmol ICV in goldfish) [8, 10, 11].

Chronic administration (mice, 12 to 14 days): No adverse events reported in diet-induced obesity treatment studies at efficacious doses [11, 21].

Renal considerations: One study reported that exogenous spexin aggravated renal ischemia-reperfusion injury in mice when administered at the time of renal ischemia and also triggered adverse effects in healthy kidneys at the dose tested [35]. This finding is preliminary and from a single laboratory, but warrants caution regarding dosing in the context of renal ischemia.

11.2 Theoretical safety considerations

Appetite suppression: Excessive spexin-mediated anorexia could produce unintended weight loss or nutritional deficiency in susceptible populations. Dose-response characterization should identify the therapeutic window between metabolic benefit and excessive appetite suppression.

Reproductive axis suppression: Given the inhibitory effects on gonadotropin secretion and ovarian steroidogenesis [16, 17], chronic spexin administration could produce hypogonadism, menstrual irregularity, or fertility impairment. This consideration is particularly relevant for reproductive-age women.

Gastrointestinal effects: The prokinetic effect through intestinal L-type calcium channel activation [23] could produce diarrhea or cramping at supratherapeutic doses.

Methionine oxidation products: If the methionine at position 7 oxidizes during storage or in vivo, the resulting methionine sulfoxide peptide may have altered receptor selectivity or produce immunogenic neoantigens upon chronic administration.

11.3 Therapeutic index considerations

The absence of formal toxicology data precludes calculation of a therapeutic index. The endogenous nature of the peptide (circulating at nanomolar concentrations in healthy humans) suggests a favorable safety profile at near-physiological replacement doses, but supraphysiological dosing for pharmacological effect (as required for obesity treatment or analgesia) has not been formally safety-tested.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five peptide or receptor-targeted candidates against spexin, evaluated on five standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile, and overall validation.

12.1 Galanin (GAL)

Mechanism: Non-selective agonist of GALR1, GALR2, and GALR3. A 29/30-amino-acid neuropeptide (species-dependent) with broad neuroendocrine and metabolic functions [25].

Novelty: Low. Galanin was identified in 1983 and is the index ligand of the galanin receptor family. It is the most extensively studied member of the superfamily.

Effect size: Galanin has potent and well-characterized effects on food intake (orexigenic at GALR1), nociception, seizure modulation, and neuroendocrine function. However, the GALR1-mediated effects (orexigenic, sedative, memory-impairing) oppose the metabolic therapeutic goals for which spexin is being developed [25].

Promising potential: Low for metabolic therapeutic development. The non-selective receptor profile produces opposing metabolic effects (GALR1-mediated orexia versus GALR2-mediated anorexia). Galanin itself is not a viable therapeutic candidate for obesity or metabolic disease.

Side-effect profile: GALR1 activation produces sedation, memory impairment, and orexigenic effects that limit therapeutic utility [25].

Overall validation: High as a biological tool and reference compound; low as a therapeutic candidate for the indications relevant to spexin.

Comparison to spexin: Spexin's GALR2/GALR3 selectivity (sparing GALR1) is its principal advantage over galanin for metabolic and analgesic therapeutic applications. Spexin lacks the GALR1-mediated sedative, memory-impairing, and orexi-genic effects of galanin.

12.2 Kisspeptin (KISS1)

Mechanism: Agonist of the kisspeptin receptor (GPR54/KISS1R). A member of the same ancestral superfamily as spexin but acting through a distinct receptor. Principal regulator of gonadotropin-releasing hormone secretion and puberty onset [19, 40].

Novelty: Moderate. The reproductive endocrine role is well established; metabolic roles are more recently characterized and represent an emerging research area.

Effect size: Kisspeptin modulates glucose-stimulated insulin secretion and food intake in animal models and humans. The effect sizes on metabolic parameters are generally modest compared to the reproductive effects, which are potent (kisspeptin administration stimulates LH pulses in humans) [40].

Promising potential: Moderate. Kisspeptin is in clinical development for reproductive applications (hypothalamic amenorrhea, IVF protocols). Metabolic applications remain preclinical.

Side-effect profile: Reproductive axis activation (premature LH surge, ovarian hyperstimulation) limits metabolic dosing in reproductive-age women. The metabolic therapeutic window is undefined.

Overall validation: High for reproductive endocrinology; low for metabolic therapeutic applications.

Comparison to spexin: Spexin and kisspeptin are ancestrally related but act through entirely distinct receptors (GALR2/3 versus KISS1R) and have largely complementary rather than overlapping physiological roles. Spexin is better positioned for metabolic and analgesic applications; kisspeptin for reproductive applications.

12.3 GLP-1 receptor agonists (semaglutide)

Mechanism: Agonist of the glucagon-like peptide-1 receptor (GLP-1R), producing insulin secretion, glucagon suppression, delayed gastric emptying, and central appetite suppression [41].

Novelty: Low for the mechanism (GLP-1 biology characterized since 1980s); high for the clinical impact (semaglutide approved 2017 for diabetes, 2021 for obesity).

Effect size: Very high. Semaglutide produces 15 to 20 percent body weight reduction in clinical trials (STEP program), the largest effect size of any approved anti-obesity pharmacotherapy [41].

Promising potential: Very high. Multiple approved indications (type 2 diabetes, obesity, cardiovascular risk reduction). Tirzepatide (dual GIP/GLP-1 agonist) extends the class further.

Side-effect profile: Nausea, vomiting, diarrhea, pancreatitis risk, potential thyroid C-cell concerns. Gastrointestinal adverse events are dose-limiting in approximately 5 to 10 percent of patients [41].

Overall validation: Very high. Extensive Phase 3 data, regulatory approval, and real-world evidence.

Comparison to spexin: GLP-1 agonists represent the gold standard for metabolic pharmacotherapy against which spexin must be evaluated. Spexin operates through a distinct receptor mechanism (GALR2/3 versus GLP-1R) and could theoretically provide additive benefit in combination. However, spexin is decades behind GLP-1 agonists in clinical validation; the preclinical effect sizes on weight loss are substantially smaller than semaglutide's clinical effect. Spexin's potential advantages are the non-opioid analgesic activity and anxiolytic effects that GLP-1 agonists lack.

12.4 Galanin receptor 2 selective agonist dN1-Qu (spexin-based)

Mechanism: GALR2-selective partial agonist derived from spexin by quadruple amino acid substitution (Gln5-Asn, Met7-Ala, Lys11-Phe, Ala13-Pro) plus D-amino acid N-terminal stabilization [5].

Novelty: Moderate-high. First rationally designed GALR2-selective agonist based on spexin scaffold.

Effect size: Anxiolytic effect comparable to diazepam in mouse elevated plus maze. Metabolic effects not yet characterized independently of native spexin [5].

Promising potential: Moderate. The compound is a research tool and lead optimization candidate. No clinical development has been initiated.

Side-effect profile: Unknown in formal toxicology. The GALR2 selectivity should spare GALR1-mediated sedation and GALR3-mediated effects, potentially improving the therapeutic index over native spexin.

Overall validation: Low. Published in 2016 with anxiolytic data; no subsequent clinical advancement reported.

Comparison to spexin: dN1-Qu is a derivative of spexin with improved receptor subtype selectivity and serum stability. It represents the first-generation optimized analog and is positioned as a tool compound for dissecting GALR2-specific pharmacology rather than as a clinical candidate in its current form.

12.5 LIT-01-144 (metabolically resistant spexin analog)

Mechanism: GALR2/GALR3 agonist with N-terminal fluorocarbon chain modification conferring metabolic resistance and peripheral restriction (no CNS penetration) [15].

Novelty: High. First metabolically stabilized spexin analog with demonstrated peripheral selectivity and in vivo non-opioid analgesic efficacy.

Effect size: Potent antinociception in CFA-induced persistent inflammatory pain at doses 10-fold lower than native spexin ICV. No effect in naive animals (pathological pain selectivity) [15].

Promising potential: Moderate-high. The non-opioid analgesic mechanism addresses a major clinical need. Pre-IND stage with patent protection. The 2026 publication date indicates active development.

Side-effect profile: Preliminary. No CNS effects (peripherally restricted). No reported adverse events at efficacious doses in mice [15].

Overall validation: Low-moderate. Single preprint publication (bioRxiv 2026). Awaits peer review, replication, and formal preclinical development.

Comparison to spexin: LIT-01-144 represents the most advanced spexin analog for therapeutic development, combining metabolic stability, receptor activity, and a clear therapeutic application (non-opioid peripheral analgesia). It addresses the principal pharmacokinetic limitation of native spexin (short half-life) and the challenge of target selectivity (peripheral restriction avoids central appetite and mood effects that might complicate an analgesic indication).

12.6 Comparator summary

The five comparators span the continuum from the ancestral endogenous ligand (galanin) through the superfamily relative (kisspeptin) to the clinically validated comparator class (GLP-1 agonists) and the spexin-derived optimized analogs (dN1-Qu, LIT-01-144). **Galanin** is pharmacologically broader but therapeutically limited by GALR1-mediated adverse effects. **Kisspeptin** addresses distinct (reproductive) rather than overlapping (metabolic) biology. **GLP-1 agonists** represent the clinical benchmark for anti-obesity pharmacotherapy and substantially exceed spexin's current evidence base. **dN1-Qu** is a first-generation receptor-selective tool compound. **LIT-01-144** is the most therapeutically promising spexin derivative, positioned for non-opioid analgesia development.

Spexin occupies a unique position as an endogenous peptide with a characterized physiological role in metabolic homeostasis, a circulating biomarker deficit in human metabolic disease, and a preclinical pharmacology spanning appetite, lipid metabolism, glucose homeostasis, nociception, anxiety, and reproduction. Its principal limitation relative to the validated comparators (GLP-1 agonists) is the complete absence of human interventional data, the short pharmacokinetic half-life of the native peptide, and the pleiotropic pharmacology that complicates indication-specific development. The analog development programs (dN1-Qu for GALR2-selective anxiolysis; LIT-01-144 for peripheral analgesia) represent rational therapeutic optimization strategies that address these limitations through receptor subtype selectivity, metabolic stabilization, and tissue restriction.

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