

Adropin

A 76-amino-acid secreted peptide discovered in 2008 by Kumar et al. through liver transcriptomic profiling of melanocortin-3 receptor-deficient mice, encoded by the Energy Homeostasis Associated (Enho) gene, and subsequently characterized as a hepatokine and neuropeptide with roles in endothelial nitric oxide synthase upregulation, glucose and lipid homeostasis, insulin sensitization, neuroprotection in experimental ischemic stroke, and anti-atherosclerotic signaling through the orphan G protein-coupled receptor GPR19 and vascular endothelial growth factor receptor 2.

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Secreted peptide hormone encoded by the Energy Homeostasis Associated (ENHO) gene with endothelial-protective, metabolic-regulatory, and neuroprotective activity

ABSTRACT

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Adropin is a 76-amino-acid secreted peptide encoded by the Energy Homeostasis Associated (Enho) gene, first identified in 2008 by Kumar et al. (Cell Metabolism) through microarray profiling of liver gene expression in melanocortin-3 receptor knockout (Mc3r-/-) mice on a C57BL/6J background [1]. The name derives from the Latin aduro (to set fire to) and pinquis (fat or greasy), reflecting the original observation that hepatic Enho expression is acutely upregulated by short-term high-fat feeding and suppressed in states of diet-induced obesity and prolonged caloric excess. The biologically active secreted domain spans amino acids 34 through 76, with residues 1 through 33 constituting a signal peptide that directs membrane anchoring and extracellular release. Human, mouse, and rat adropin amino acid sequences are 100 percent identical, a degree of conservation unusual among metabolic peptides and suggestive of strong functional constraint across mammalian species. The mature peptide has a molecular weight of approximately 4,499 daltons and functions both as a soluble circulating factor and as a membrane-bound protein facilitating intercellular communication through the Notch signaling pathway in the central nervous system. The biological effects of adropin are mediated principally through two receptor systems: the orphan G protein-coupled receptor 19 (GPR19), which couples to downstream MAPK and Akt signaling cascades in cardiomyocytes and other cell types; and vascular endothelial growth factor receptor 2 (VEGFR2), through which adropin upregulates endothelial nitric oxide synthase (eNOS) expression via the PI3K-Akt and ERK1/2 pathways to promote nitric oxide release,

endothelial cell proliferation, migration, and capillary tube formation. Lovren et al. (2010) demonstrated in Circulation that adropin-treated human umbilical vein endothelial cells exhibited enhanced proliferation, migration, and tube formation with reduced permeability and tumor necrosis factor-induced apoptosis [2]. In the original Kumar et al. characterization, transgenic overexpression or systemic adropin treatment in diet-induced obese mice attenuated hepatosteatosis and insulin resistance independently of effects on adiposity or food intake, with adropin regulating expression of hepatic lipogenic genes (fatty acid synthase, stearoyl-CoA desaturase 1) and adipose tissue peroxisome proliferator-activated receptor gamma [1]. Preclinical pharmacology has expanded substantially beyond metabolic endpoints: in experimental ischemic stroke models, synthetic adropin administered intravenously at 900 to 2,700 nmol/kg at the onset of or up to 3 hours after permanent middle cerebral artery occlusion dose-dependently reduced infarct size, blood-brain barrier disruption, tight junction protein degradation, matrix metalloproteinase-9 activity, oxidative stress, and neutrophil infiltration through an eNOS-dependent mechanism, as adropin therapy failed to confer neuroprotection in eNOS-deficient mice [3, 4]. Additional preclinical work has demonstrated anti-atherosclerotic activity through suppression of monocyte-endothelial cell adhesion and smooth muscle cell proliferation [5], preservation of the blood-brain barrier after intracerebral hemorrhage through a Notch1/Hes1 pathway [6], and restoration of cardiac glucose oxidation in pre-diabetic obese mice through modulation of the mitochondrial acetyltransferase GCN5L1 [7]. Clinical studies in humans are predominantly observational: serum adropin levels are consistently and significantly lower in patients with coronary artery disease, acute myocardial infarction,

metabolic syndrome, type 2 diabetes mellitus, polycystic ovary syndrome, and obstructive sleep apnea compared to healthy controls, with inverse correlations between adropin concentration and disease severity scores including the SYNTAX score for coronary atherosclerotic burden [8, 9, 10]. A meta-analysis by Zheng et al. (2019) encompassing 7 case-control studies with 525 coronary artery disease patients and 420 controls confirmed the consistent inverse association [8]. No human interventional trials of exogenous adropin administration have been published as of the most recent monograph revision. The compound is available as a synthetic research peptide from multiple suppliers (Phoenix Pharmaceuticals, Bachem, Creative Peptides, GenScript) typically as adropin (34-76), the biologically active fragment, at greater than 95 percent purity by HPLC. This monograph reviews the discovery and gene characterization; the amino acid sequence, structure, and synthesis; the dual-receptor molecular pharmacology through GPR19 and VEGFR2-eNOS; the tissue distribution and nutritional regulation of Enho expression; the preclinical pharmacology across metabolic, cardiovascular, and neurological models; the clinical observational evidence base; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events and safety considerations; and a comparative assessment of five metabolic-regulatory peptide candidates (irisin, FGF21, GDF15, apelin, MOTS-c) against adropin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Peptide name: Adropin.

Gene name: Energy Homeostasis Associated (ENHO); mouse ortholog Enho. The gene symbol is the canonical identifier in the genomic and metabolic literature.

UniProt accession: Q6UWT2 (human ENHO precursor protein, 76 amino acids).

NCBI Gene ID: 375704 (human ENHO).

IUPHAR/BPS Guide to Pharmacology ligand ID: 9573.

Synonyms: Adropin (34-76) refers specifically to the secreted biologically active fragment used in most research preparations; the full-length 76-amino-acid precursor is sometimes designated adropin (1-76).

Chemical Abstracts Service registry number: No CAS number has been formally assigned to the full-length or truncated adropin peptide in the Chemical Abstracts registry as of the most recent monograph revision. The peptide is identified in commercial catalogs by proprietary catalog numbers (Phoenix Pharmaceuticals catalog 079-62; Bachem custom synthesis; GenScript custom synthesis).

1.2 Structural class and chemistry

Adropin is a short secreted peptide of the hepatokine and neuropeptide class. It does not belong to any established peptide hormone superfamily (insulin, glucagon, natriuretic, incretin) and has no significant sequence homology to other known mammalian peptides, placing it as an orphan peptide with a novel structural class [1, 11].

Amino acid sequence (human, full-length, 76 residues):
MGAAISQGALIAIVCNGLVGFLLLLWVILCWACHSR SADVDSLSESPNSSPGPCPEKAP
PPQKPSHEG SYLLQP

Residues 1 through 33 constitute the signal peptide, which contains a short cytoplasmic N-terminal domain (residues 1-9), a hydrophobic transmembrane-spanning region (residues 9-30), and a signal peptidase cleavage site yielding the secreted mature peptide at residue 34 [11, 12].

Mature secreted peptide: Adropin (34-76), 43 amino acids: HRSADVDLSLESSPNSSPGPCPEKAP PPQKPSHEG SYLLQP.

Molecular weight: Approximately 4,499 daltons for the mature secreted peptide (34-76). The full-length precursor (1-76) has a calculated molecular weight of approximately 7,800 daltons.

Molecular formula: The mature peptide (34-76) has an approximate molecular formula reflecting 43 amino acids with the specific sequence composition; exact formula depends on the charged state and terminal modifications of the synthetic preparation.

Physical properties: Supplied as a white to off-white lyophilized powder. Soluble in water and aqueous buffers at neutral to mildly acidic pH. Contains a single cysteine residue at position 51 of the full-length sequence (position 18 of the mature peptide), which can participate in disulfide bond formation under non-reducing conditions.

Species conservation: The amino acid sequence of adropin is 100 percent identical across human, mouse, and rat, a conservation level exceeded by very few peptide hormones of comparable length and consistent with strong purifying selection on the mature secreted domain [1, 12].

1.3 Synthesis

Adropin for research use is produced by solid-phase peptide synthesis using standard Fmoc (9-fluorenylmethyloxycarbonyl) chemistry. The 43-amino-acid mature peptide (34-76) is the standard synthetic target; full-length 76-residue preparations are less common and are typically produced for structural studies or antibody generation.

Synthesis proceeds from the C-terminal proline residue on a resin support, with sequential Fmoc-protected amino acid coupling, deprotection, and cleavage. The single cysteine residue requires trityl or acetamidomethyl side-chain protection during synthesis and careful handling during cleavage and purification to avoid ox-

idative dimerization. Purification is by preparative reverse-phase high-performance liquid chromatography, with identity confirmation by electrospray ionization mass spectrometry or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Typical research-grade preparations are supplied at greater than 95 percent purity by analytical HPLC.

No total chemical synthesis of adropin has been published in a dedicated synthetic methodology paper; the compound is produced by standard peptide synthesis service laboratories and by the commercial suppliers listed below.

2. Abstract

Adropin is a 76-amino-acid secreted peptide encoded by the Energy Homeostasis Associated (Enho) gene, discovered in 2008 by Kumar et al. through microarray-based transcriptomic analysis of liver tissue in melanocortin-3 receptor knockout mice [1]. The peptide has since been characterized as a multifunctional regulatory factor with established roles in energy homeostasis, lipid metabolism, glucose utilization, endothelial function, cardiovascular protection, and neuroprotection. Its biological effects are mediated through at least two receptor systems: the orphan G protein-coupled receptor GPR19, through which adropin modulates MAPK-mediated phosphorylation and cardiac fuel metabolism [7, 13]; and vascular endothelial growth factor receptor 2 (VEGFR2), through which adropin activates the PI3K-Akt and ERK1/2 signaling cascades to upregulate endothelial nitric oxide synthase (eNOS) and promote nitric oxide-dependent vascular protection [2, 3].

The original discovery established that hepatic Enho expression is nutritionally regulated: short-term high-fat feeding acutely increases expression, while prolonged dietary obesity suppresses it, creating a deficiency state associated with insulin resistance and hepatosteatosis [1]. Transgenic overexpression or exogenous adropin administration in diet-induced obese mice reversed these metabolic derangements independently of changes in body weight or food intake, establishing adropin as a hepatokine with direct metabolic regulatory activity.

Subsequent preclinical work has expanded the pharmacological profile substantially. Lovren et al. (2010) demonstrated that adropin is a novel regulator of endothelial function, with adropin-treated human umbilical vein endothelial cells showing enhanced proliferation, migration, and capillary tube formation alongside reduced permeability and apoptosis [2]. In experimental ischemic stroke, synthetic adropin administered intravenously dose-dependently reduced infarct size through an eNOS-dependent mechanism, with therapeutic benefit preserved when administration was delayed to 3 hours post-occlusion [3, 4]. Anti-atherosclerotic activity has been demonstrated through suppression of monocyte-endothelial adhesion and vascular smooth muscle cell proliferation [5]. Cardiac metabolic effects include restoration of glucose oxidation in pre-diabetic hearts through modulation of the mitochondrial acetyltransferase GCN5L1 [7].

Clinical evidence is exclusively observational. Serum adropin levels are consistently reduced in patients with coronary artery disease, acute myocardial infarction, type 2 diabetes, metabolic syndrome, polycystic ovary syndrome, non-alcoholic fatty liver disease, and obstructive sleep apnea [8, 9, 10, 14, 15]. The inverse association between circulating adropin and cardiovascular risk has been confirmed by meta-analysis [8]. No interventional clinical trials of exogenous adropin administration in humans have been conducted or registered. The compound is currently positioned as a preclinical research tool and a candidate biomarker, not as a therapeutic agent.

3. Discovery and Development History

3.1 Origin

Adropin was identified in 2008 by Ganesh Kumar and colleagues at Saint Louis University in a study published in *Cell Metabolism* [1]. The discovery arose from microarray analysis of hepatic gene expression in C57BL/6J mice lacking the melanocortin-3 receptor (Mc3r^{-/-}), a model of metabolic dysfunction characterized by increased adiposity and impaired metabolic flexibility. Among the differentially expressed transcripts, Kumar et al. identified a previously uncharacterized open reading frame encoding a 76-amino-acid peptide with a predicted signal peptide sequence, suggesting secretion. The gene was named Energy Homeostasis Associated (Enho) on the basis of its nutritional regulation and metabolic phenotype, and the encoded peptide was named adropin from the Latin *aduro* (to set fire to) and *pinquis* (fat), reflecting its association with lipid oxidation and energy expenditure.

3.2 Early metabolic characterization

The original Kumar et al. report established several foundational observations. First, hepatic Enho mRNA was acutely upregulated (approximately 3- to 5-fold) in lean mice placed on a high-fat diet for up to one month, but was suppressed in mice with established diet-induced obesity, suggesting that adropin functions as an acute metabolic sensor whose expression is lost in chronic overnutrition. Second, fasting reduced hepatic Enho expression compared to ad libitum-fed controls. Third, transgenic mice overexpressing adropin (AdrTg) on a high-fat diet were protected from hepatosteatosis and insulin resistance despite comparable adiposity to wild-type controls. Fourth, systemic administration of synthetic adropin to diet-induced obese wild-type mice reproduced the metabolic protection, reducing hepatic lipogenic gene expression (Fasn, Scd1) and improving insulin sensitivity without affecting food intake or body weight [1].

3.3 Endothelial function discovery

The second major advance was the Lovren et al. (2010) report in *Circulation* demonstrating that adropin is a regulator of endothelial function [2]. Using human umbilical vein endothelial cells, Lovren et al. showed that adropin treatment upregulated eNOS expression through VEGFR2 activation and the downstream PI3K-Akt and ERK1/2 pathways. The functional consequences included enhanced endothelial cell proliferation, migration, capillary-like tube formation, and reduced permeability and TNF-alpha-induced apoptosis. In a murine hindlimb ischemia model, adropin promoted revascularization and blood flow recovery. This report established adropin as a cardiovascular-relevant peptide beyond its original metabolic context.

3.4 Identification of GPR19 as a putative receptor

The identification of GPR19 as a receptor for adropin was advanced by Stein et al. (2016) and subsequently supported by the Bhatt laboratory and others [13, 16]. GPR19 is an orphan G protein-coupled receptor expressed in brain, heart, and peripheral tissues. Knockdown of GPR19 in cardiomyocytes blocked the effects of adropin on pyruvate dehydrogenase kinase 4 (PDK4) expression and cardiac fuel metabolism, providing functional evidence for receptor-ligand pairing. The designation remains putative, as the direct binding affinity and selectivity of adropin for GPR19 have not been fully characterized by radioligand displacement or surface plasmon resonance, and alternative or additional receptor interactions (VEGFR2, Notch pathway components) contribute to the signaling profile in different cell types.

3.5 Expansion to neuroprotection

Beginning in 2017, the Bhatt and Bhatt laboratory at the University of Florida extended the adropin pharmacology to experimental stroke. A series of publications demonstrated that synthetic adropin administered intravenously at 900 to 2,700 nmol/kg reduced infarct size, blood-brain barrier damage, and neurological deficit scores in permanent middle cerebral artery occlusion models, with effect preserved at a 3-hour delay post-occlusion [3, 4]. The mechanism was eNOS-dependent: adropin therapy was protective in wild-type mice but failed to confer benefit in eNOS knockout mice. Subsequent work extended the neuroprotective profile to in-

tracerebral hemorrhage through a Notch1/Hes1 pathway mediating blood-brain barrier preservation [6], and to subarachnoid hemorrhage through sustained eNOS Ser1179 phosphorylation [17].

3.6 Current research-clinical state

As of the most recent monograph revision, adropin remains a preclinical research compound and a candidate circulating biomarker. No interventional clinical trials of exogenous adropin have been registered or published. The compound is not in commercial pharmaceutical development. The research trajectory is active, with approximately 200 publications indexed in PubMed as of 2026, the majority in metabolic, cardiovascular, and neurological domains. The principal unresolved questions are the definitive receptor pharmacology (GPR19 versus alternative receptors), the pharmacokinetic profile of synthetic adropin in humans, and the feasibility of therapeutic peptide administration for the metabolic and neuroprotective indications suggested by preclinical data.

4. Mechanism of Action

Adropin is a multifunctional secreted peptide whose biological activities are mediated through at least two receptor systems and through direct membrane-associated intercellular signaling. The principal downstream effects are endothelial nitric oxide synthase upregulation, metabolic fuel switching from fatty acid to glucose oxidation, anti-inflammatory signaling, and neuroprotection.

4.1 GPR19-mediated signaling

The orphan G protein-coupled receptor GPR19 has been identified as a putative receptor for adropin on the basis of functional studies in cardiomyocytes and neuronal cells [13, 16]. In cardiomyocytes, adropin activates GPR19 to induce MAPK-mediated phosphorylation cascades that regulate expression of pyruvate dehydrogenase kinase 4 (PDK4), a mitochondrial gatekeeper enzyme that when active inhibits the pyruvate dehydrogenase complex and thereby suppresses glucose oxidation [7]. Adropin-induced GPR19 activation suppresses PDK4, relieving the inhibition on pyruvate dehydrogenase and shifting cardiac fuel metabolism from fatty acid oxidation toward glucose oxidation. The effect is mediated through modulation of the mitochondrial acetyltransferase GCN5L1, which alters the acetylation status of fuel metabolism enzymes. Knockdown of GPR19 by small interfering RNA *in vitro* abolished the adropin effect on PDK4, providing functional evidence for the receptor-ligand relationship [7, 13].

In the brain, GPR19 is expressed in the hypothalamus and in regions involved in fluid balance and autonomic regulation. Stein et al. (2016) demonstrated that intracerebroventricular adropin injection inhibited water drinking in rats, an effect that was associated with GPR19 expression in the subfornical organ [16]. The central nervous system GPR19 pathway is a candidate mechanism for the autonomic and behavioral effects of adropin, including regulation of physical activity and motor coordination.

4.2 VEGFR2-eNOS endothelial signaling

The second principal signaling axis is the VEGFR2-mediated upregulation of eNOS in endothelial cells. Lovren et al. (2010) established that adropin increases eNOS protein expression and phosphorylation at Ser1177 (the activating site) through upstream activation of VEGFR2 with resultant engagement of the PI3K-Akt and ERK1/2 kinase cascades [2]. The net effect is increased nitric oxide bioavailability, which mediates endothelial cell survival, proliferation, migration, angiogenesis, and vasodilation.

VEGFR2 was required for adropin signaling in both cardiac and non-cardiac endothelial cells, suggesting that VEGFR2 may act as a co-receptor or alternative receptor for adropin in the vascular compartment [18]. The relationship between GPR19 and VEGFR2 in adropin signaling is not fully resolved; it is possible that GPR19 activation leads to VEGFR2 transactivation, or that adropin engages each receptor independently depending on cell type and local expression patterns.

The eNOS-dependent mechanism is the molecular basis for the neuroprotective effects of adropin in experimental stroke: the Bhatt laboratory demonstrated that adropin therapy was protective in wild-type mice but failed to reduce brain injury in eNOS-deficient animals, establishing eNOS as the obligate downstream effector [3].

4.3 Notch signaling in the central nervous system

In the central nervous system, adropin also functions as a membrane-bound protein that interacts with NB3 (contactin-6), a brain-specific Notch1 ligand [6, 12]. Through this interaction, adropin modulates the Notch1/Hes1 signaling pathway, which regulates cell fate decisions, neuronal differentiation, and blood-brain barrier integrity. The Notch-mediated mechanism is distinct from the GPR19 and VEGFR2 pathways and is the basis for the blood-brain barrier preservation observed in experimental intracerebral hemorrhage models [6].

4.4 Metabolic signaling

The metabolic actions of adropin encompass several downstream pathways:

Insulin signaling enhancement: adropin increases phosphorylation of Akt (protein kinase B) and promotes translocation of glucose transporter 4 (GLUT4) to the plasma membrane in skeletal muscle, enhancing insulin-stimulated glucose uptake [1, 19].

Hepatic lipogenesis suppression: adropin downregulates expression of fatty acid synthase (Fasn), stearoyl-CoA desaturase 1 (Scd1), and sterol regulatory element-binding protein 1c (Srebp1c) in the liver, reducing de novo lipogenesis and hepatic triglyceride accumulation [1].

Peroxisome proliferator-activated receptor gamma regulation: in adipose tissue, adropin modulates PPARgamma activity, influencing adipocyte differentiation and lipid storage [1].

Cardiac fuel metabolism: as noted above, adropin shifts cardiac fuel preference from fatty acid to glucose oxidation through GPR19-mediated PDK4 suppression and GCN5L1 modulation [7].

4.5 Anti-inflammatory and anti-atherosclerotic mechanisms

Adropin suppresses monocyte-endothelial cell adhesion by reducing expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells, and inhibits vascular smooth muscle cell proliferation, two key processes in atherogenesis [5]. In ApoE^{-/-}/Enho^{-/-} double-knockout mice, adropin deficiency accelerated atherosclerosis progression through enhanced endothelial-to-mesenchymal transition, and exogenous adropin treatment reversed this effect [20]. The anti-inflammatory activity is consistent with the observed reduction of TNF-alpha-induced endothelial apoptosis reported by Lovren et al. [2] and with emerging evidence linking adropin to regulation of immune cell homeostasis [21].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and plasma levels

The pharmacokinetics of exogenous synthetic adropin in humans have not been formally characterized. No published human pharmacokinetic study of administered adropin peptide exists as of the most recent monograph revision. Endogenous circulating adropin levels in healthy human adults have been measured by enzyme-linked immunosorbent assay (ELISA) in multiple observational studies, with reported concentrations varying substantially across studies owing to differences in ELISA kit specificity, antibody epitope, sample processing, and calibration standards.

Representative reported values include approximately 3.0 to 8.0 ng/mL in healthy controls in studies using the Phoenix Pharmaceuticals ELISA kit [10, 14], and approximately 50 to 70 pg/mL in studies using alternative assay platforms [9]. The variability in absolute values across publications is a recognized methodological limitation; relative comparisons within individual studies (cases versus controls) are more reliable than cross-study comparisons of absolute concentrations.

5.2 Half-life

The plasma half-life of adropin has not been directly measured. As a small peptide of 43 amino acids (mature form) without known post-translational modifications that would confer protease resistance (glycosylation, PEGylation, albumin binding), the half-life is presumed to be short, in the range of minutes to tens of minutes, consistent with other unmodified circulating peptides of comparable size [11, 22]. This presumptive short half-life has implications for the design of any future therapeutic application: sustained-release formulations, peptide modifications for protease resistance, or continuous infusion protocols would likely be required to maintain pharmacologically active plasma concentrations.

5.3 Distribution

Adropin is expressed in and detected in multiple tissues: liver (the principal peripheral source), brain (with particularly high expression in the hypothalamus, cerebellum, and midbrain), heart, kidney, pancreas, small intestine, endothelial cells, and colostrum [1, 11, 12]. The tissue distribution of the ENHO gene product is broader than the initial liver-brain characterization suggested; subsequent studies have detected Enho mRNA and adropin protein immunoreactivity in vascular endothelium, coronary arteries, umbilical vein, and immune cells.

Adropin crosses the blood-brain barrier, as demonstrated by central nervous system effects following systemic (intravenous) administration of synthetic adropin in stroke and hemorrhage models [3, 4, 6]. Whether this reflects direct peptide transport, receptor-mediated transcytosis, or action on luminal endothelial targets with secondary central effects has not been definitively resolved.

5.4 Metabolism and elimination

The metabolic fate of circulating adropin has not been characterized. Degradation by plasma proteases (aminopeptidases, endopeptidases) is the presumed principal clearance mechanism, consistent with other small unmodified peptides. Renal filtration and clearance of the intact peptide or its fragments is also likely given the molecular weight (approximately 4,499 daltons, below the glomerular filtration threshold).

5.5 Routes of administration

In preclinical research, adropin has been administered by:

Intravenous injection: the principal route in stroke and hemorrhage models, with doses of 90 to 2,700 nmol/kg in mice [3, 4].

Intraperitoneal injection: used in metabolic studies in mice, with doses of 450 nmol/kg twice daily for up to 18 days [1].

Intracerebroventricular injection: used in central nervous system pharmacology studies [16].

Osmotic minipump infusion: used for sustained delivery in some metabolic studies.

No oral bioavailability data exist; as a peptide, adropin is presumed to have negligible oral bioavailability owing to gastrointestinal proteolysis.

5.6 Nutritional regulation of endogenous levels

Endogenous adropin production is regulated by dietary macronutrient composition and caloric status. Hepatic *Enho* expression increases acutely with high-fat feeding in lean mice and decreases with fasting [1]. In established obesity, *Enho* expression is suppressed, creating a deficiency state. Serum adropin levels in Rhesus macaques exhibit diurnal variation, with higher expression during daytime [23]. In humans, circulating adropin levels are inversely associated with body mass index, insulin resistance (HOMA-IR), and triglyceride levels in most published cross-sectional studies [14, 15]. Physical exercise (aerobic training) increases serum adropin levels independently of weight loss in obese adolescents [24].

The regulatory inputs controlling *ENHO* transcription include liver X receptor alpha (LXRalpha), retinoic acid receptor-related orphan receptor (ROR), estrogen receptor alpha (ERalpha), signal transducer and activator of transcription 3 (STAT3), and glucagon-like peptide-1 (GLP-1) signaling [11, 22].

6. Preclinical Pharmacology

6.1 Metabolic models

The foundational metabolic pharmacology was established in the Kumar et al. (2008) report. Systemic adropin administration (450 nmol/kg intraperitoneally, twice daily for 14 to 18 days) to diet-induced obese C57BL/6J mice reduced hepatic triglyceride content, downregulated hepatic lipogenic genes (Fasn, Scd1, Srebp1c), improved glucose tolerance and insulin sensitivity as measured by glucose and insulin tolerance tests, and reduced fasting hyperinsulinemia [1]. These effects occurred without changes in food intake, body weight, or adipose tissue mass, indicating a direct metabolic regulatory mechanism rather than an anorexigenic or body-composition effect.

Subsequent studies confirmed and extended these findings. Gao et al. (2015) demonstrated that adropin treatment improved glucose utilization and insulin sensitivity in aged mice, with enhanced Akt phosphorylation and GLUT4 membrane translocation in skeletal muscle [19]. In nonhuman primates, Butler et al. (2019) showed that low baseline plasma adropin concentrations predicted greater weight gain and metabolic dysregulation (dyslipidemia, insulin resistance) in response to a high-sugar diet, establishing adropin as a predictive biomarker for metabolic vulnerability in a species closely related to humans [23].

6.2 Cardiovascular models

Lovren et al. (2010) demonstrated the endothelial-protective pharmacology in vitro and in vivo. In human umbilical vein endothelial cells, adropin enhanced proliferation, migration, and tube formation while reducing permeability and TNF-alpha-induced apoptosis through VEGFR2-PI3K-Akt-eNOS signaling [2]. In a murine hindlimb ischemia model, adropin promoted revascularization and blood flow recovery.

Sato et al. (2018) showed that adropin contributes to anti-atherosclerosis by suppressing monocyte-endothelial cell adhesion (via downregulation of ICAM-1 and VCAM-1) and smooth muscle cell proliferation in vitro and in ApoE knockout mice [5]. Chen et al. (2023) extended the anti-atherosclerotic work using ApoE^{-/-}/Enho^{-/-}

double-knockout mice, demonstrating that adropin deficiency accelerated atherosclerosis through enhanced endothelial-to-mesenchymal transition and that exogenous adropin reversed this process [20].

Altamimi et al. (2019) showed that acute adropin treatment (intravenous bolus) restored cardiac glucose oxidation in hearts from pre-diabetic obese mice by suppressing PDK4 expression and modulating GCN5L1-mediated acetylation of fuel metabolism enzymes, with the effect dependent on GPR19 [7]. Subsequent work by the same group found that diet-induced obese mice with established obesity were partially resistant to short-term adropin cardiac benefits, suggesting that prolonged metabolic derangement may attenuate the therapeutic window [25].

6.3 Neuroprotection models

The Bhatt laboratory produced a series of reports demonstrating profound neuroprotection by synthetic adropin in experimental stroke:

Yang et al. (2017) reported that intravenous adropin (900 nmol/kg) administered at the onset of permanent middle cerebral artery occlusion in C57BL/6J mice reduced infarct size by approximately 45 to 50 percent at 48 hours, with associated reductions in brain edema, blood-brain barrier permeability, and neurological deficit scores [4].

Yang et al. (2021) extended these findings in a comprehensive dose-response and mechanistic study published in *Redox Biology*, demonstrating that adropin at 90, 900, and 2,700 nmol/kg dose-dependently reduced infarct size; that 3-hour delayed administration preserved the protective effect; that adropin increased eNOS Ser1177 phosphorylation and reduced matrix metalloproteinase-9 activity, oxidative stress, and neutrophil infiltration; and that the neuroprotection was abolished in eNOS knockout mice [3].

Yang et al. (2017) also demonstrated that adropin preserved the blood-brain barrier after intracerebral hemorrhage through activation of the Notch1/Hes1 signaling pathway, reducing brain edema and improving neurological outcomes [6].

Dodd et al. (2024) extended the neuroprotective pharmacology to subarachnoid hemorrhage, showing that synthetic adropin treatment reduced neurobehavioral deficits through sustained Ser1179 phosphorylation of eNOS [17].

6.4 Systematic review of preclinical dosing

A systematic review by Mushala and Gandy (2021) evaluated optimal therapeutic adropin dose intervention across published mouse and rat studies [26]. The review identified effective dose ranges of 450 to 2,700 nmol/kg for intravenous or intraperitoneal routes, with the most consistent metabolic effects at 450 nmol/kg twice daily for 14 to 18 days (metabolic models) and the most consistent neuroprotective effects at 900 to 2,700 nmol/kg as a single intravenous dose (stroke models). The review noted the absence of formal dose-finding studies, toxicology assessments, and pharmacokinetic characterization as limitations of the existing preclinical literature.

7. Clinical Evidence Base

7.1 Coronary artery disease

Multiple observational studies have consistently reported lower serum adropin levels in patients with coronary artery disease (CAD) compared to healthy controls. Wu et al. (2014) reported that serum adropin in a cohort of 116 patients with stable CAD was significantly lower than in 116 age-matched controls (59.2 +/- 19.3 versus 70.0 +/- 18.2 pg/mL) [9]. Celik et al. (2013) found lower adropin in CAD patients (1.91 versus 3.19 ng/mL in controls), with adropin levels inversely correlated with the number of diseased coronary vessels [27]. Ertem et al. (2016) demonstrated that serum adropin was an independent predictor of high SYNTAX score in patients with non-ST elevation myocardial infarction, with lower adropin levels predicting more severe and diffuse coronary atherosclerosis [28].

The Zheng et al. (2019) meta-analysis pooled 7 case-control studies encompassing 525 CAD patients and 420 controls and confirmed a statistically significant reduction in serum adropin in the CAD group, with a standardized mean difference of approximately -1.2 (95 percent confidence interval -1.8 to -0.6), supporting adropin as a consistent inverse biomarker of coronary atherosclerotic burden [8].

7.2 Acute myocardial infarction

Serum adropin levels are reduced in patients with acute myocardial infarction (AMI) compared to stable CAD and healthy controls. Yu et al. (2014) reported that adropin levels at admission independently predicted 30-day major adverse cardiovascular events in AMI patients, with lower adropin associated with larger infarct size and worse outcomes [29]. Subsequent studies have confirmed the prognostic value of adropin in acute coronary syndromes.

7.3 Type 2 diabetes and metabolic syndrome

Reduced circulating adropin has been reported in patients with type 2 diabetes mellitus (T2DM) and metabolic syndrome. Butler et al. (2012) demonstrated that plasma adropin concentrations were lower in T2DM patients and inversely corre-

lated with HOMA-IR, HbA1c, and triglyceride levels [14]. Topuz et al. (2013) reported similar findings in metabolic syndrome, with adropin levels correlating inversely with waist circumference, blood pressure, and insulin resistance [15]. A 2026 study by Amin et al. in Scientific Reports confirmed that adropin, along with asprosin and irisin, serves as a potential biomarker for cardiovascular risk stratification in diabetes and prediabetes [30].

7.4 Obstructive sleep apnea

Celik et al. (2018) reported that plasma adropin levels were significantly lower in patients with severe obstructive sleep apnea (OSA) compared to moderate OSA and controls (4.50 +/- 1.45 versus 6.55 +/- 1.68 versus 8.15 +/- 1.79 ng/mL), with adropin levels inversely correlated with the apnea-hypopnea index and positively correlated with glucose metabolism parameters [10].

7.5 Other clinical associations

Reduced adropin has been reported in non-alcoholic fatty liver disease, polycystic ovary syndrome, preeclampsia, gestational diabetes, chronic kidney disease, and heart failure, though the individual study cohorts are generally small and the evidence base is observational [22, 31]. In heart failure, paradoxically elevated adropin levels have been reported with increasing functional class, possibly reflecting a compensatory response [32].

7.6 Limitations of the clinical evidence

The clinical evidence for adropin is entirely observational. No randomized controlled trials, interventional studies, or dose-finding studies of exogenous adropin in humans have been published. The observational associations do not establish causality: reduced adropin may be a consequence rather than a cause of metabolic and cardiovascular disease. ELISA assay variability across studies limits cross-study comparison of absolute adropin concentrations. The absence of human pharmacokinetic data, formal toxicology, and regulatory-grade manufacturing represents a substantial gap between the preclinical pharmacology and any future therapeutic application.

8. Sourcing and Quality Verification

Synthetic adropin is available from multiple peptide research suppliers as the biologically active mature fragment adropin (34-76), a 43-amino-acid peptide:

Phoenix Pharmaceuticals (catalog 079-62): the most widely cited commercial source in the research literature, supplied as lyophilized powder at greater than 95 percent purity by HPLC.

Bachem: custom synthesis available at research and GMP-adjacent grades.

GenScript: custom synthesis with standard and high-purity options.

Creative Peptides: catalog and custom synthesis options.

Sigma-Aldrich/MilliporeSigma: research-grade preparations available in select catalogs.

Typical pricing is in the range of \$150 to \$500 per milligram at research scale, reflecting the moderate synthesis difficulty of a 43-residue peptide with a single cysteine.

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

High-performance liquid chromatography area-percent purity, ideally greater than 95 percent.

Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ for the 43-amino-acid mature peptide).

Amino acid analysis to confirm composition.

Endotoxin testing (limulus amebocyte lysate or recombinant factor C assay) for preparations intended for in vivo administration, targeting less than 0.25 EU/mg.

Peptide content determination (net peptide content by amino acid analysis or nitrogen analysis, as lyophilized peptides typically contain 50 to 80 percent peptide by weight with the remainder being counter-ions, residual water, and residual trifluoroacetic acid from HPLC purification).

The adropin research peptide market is small relative to more established research peptides; lot-to-lot variability in synthetic peptides is intrinsic to the manufacturing process and on-receipt analytical confirmation is appropriate.

9. Reconstitution and Handling

Adropin (34-76) is supplied as a lyophilized powder and requires reconstitution before use.

Reconstitution for in vitro studies: Dissolve in sterile deionized water, phosphate-buffered saline (pH 7.4), or dimethyl sulfoxide (for stock solutions requiring higher concentration). The peptide is freely soluble in aqueous solutions at neutral pH at concentrations up to approximately 1 mg/mL. For DMSO stocks, prepare at 1 to 10 mg/mL and dilute into aqueous assay buffer immediately before use; final DMSO concentration in cell culture should not exceed 0.1 percent.

Reconstitution for in vivo studies: Dissolve in sterile normal saline (0.9 percent sodium chloride) or phosphate-buffered saline. For intravenous administration, filter-sterilize through a 0.22-micrometer syringe filter. Prepare doses fresh on the day of administration or from aliquoted frozen stocks.

Storage of lyophilized powder: Store desiccated at -20 degrees Celsius for routine storage (stable for 12 months or longer) or at -80 degrees Celsius for extended archival storage. Protect from moisture; allow the vial to equilibrate to room temperature before opening to minimize condensation and moisture uptake.

Storage of reconstituted solutions: Aqueous solutions should be aliquoted into single-use volumes, snap-frozen in liquid nitrogen or on dry ice, and stored at -20 or -80 degrees Celsius. Avoid repeated freeze-thaw cycles (stability demonstrated to approximately 3 cycles without significant degradation for most small peptides; formal freeze-thaw stability data specific to adropin have not been published). Reconstituted solutions stored at 2 to 8 degrees Celsius should be used within 7 days.

Handling precautions: Standard peptide handling practices apply. Work in a clean environment. Avoid exposure to strong oxidizing agents (the single cysteine residue is susceptible to oxidation). Solutions at neutral pH are stable under standard laboratory lighting; prolonged UV exposure should be avoided.

10. Stack Interaction Considerations

Adropin has not been studied in formal drug-drug interaction protocols. The following considerations are based on the known pharmacology and signaling pathways:

eNOS-modulating agents: Concurrent administration with other eNOS activators (statins via eNOS upregulation, phosphodiesterase-5 inhibitors, L-arginine) may produce additive nitric oxide-dependent vasodilation and endothelial effects. The combination has not been studied but is pharmacologically plausible and may produce additive hypotensive effects.

Insulin and insulin sensitizers: Adropin enhances insulin-stimulated glucose uptake through Akt-GLUT4 signaling. Concurrent use with exogenous insulin, metformin, thiazolidinediones, or GLP-1 receptor agonists may produce additive glucose-lowering effects. Investigators conducting metabolic studies with adropin in animals receiving concurrent insulin sensitizers should monitor for hypoglycemia.

Anti-atherosclerotic agents: Adropin suppresses endothelial adhesion molecule expression and smooth muscle cell proliferation. Combination with statins (which independently reduce ICAM-1 and VCAM-1 expression), antiplatelet agents, or anti-inflammatory biologics may produce additive anti-atherogenic effects. The combination has not been formally studied.

GLP-1 receptor agonists: GLP-1 signaling is an upstream regulator of ENHO gene expression. Concurrent GLP-1 receptor agonist therapy may increase endogenous adropin production, potentially producing additive metabolic and cardiovascular effects.

Notch pathway modulators: In the central nervous system, adropin signals through Notch1/Hes1. Concurrent use with gamma-secretase inhibitors (which block Notch processing) would be expected to attenuate the central neuroprotective effects of adropin. This interaction is relevant for investigators studying adropin in neurological models.

Other metabolic peptides: Concurrent administration with irisin, FGF21, MOTSc, or apelin has not been studied but may produce complementary or synergistic metabolic effects given the non-overlapping receptor pharmacology and partially overlapping downstream signaling.

11. Adverse Events and Safety

11.1 Preclinical safety

No formal toxicology studies of adropin have been published. The published pre-clinical literature reports no overt toxicity at the doses used in metabolic studies (450 nmol/kg intraperitoneally twice daily for up to 18 days) or in stroke models (up to 2,700 nmol/kg intravenously as a single dose) [1, 3, 4, 26]. Animals receiving adropin in published studies showed no reported adverse behavioral effects, weight loss, organ pathology, or mortality attributable to the peptide. However, the absence of formal dose-limiting toxicity studies, maximum tolerated dose determination, and chronic toxicity assessment represents a significant gap in the safety characterization.

11.2 Theoretical safety considerations

Hypoglycemia: Given the insulin-sensitizing and glucose-utilization-enhancing effects of adropin, excessive doses or concurrent insulin therapy could theoretically produce hypoglycemia, particularly in fasting states.

Hypotension: The eNOS-upregulating and vasodilatory activity of adropin could produce excessive blood pressure reduction at high doses or in combination with other vasodilatory agents.

Angiogenesis: The pro-angiogenic effects of adropin (endothelial cell proliferation, migration, tube formation, revascularization) are therapeutically desirable in ischemic conditions but could theoretically be undesirable in the context of malignancy, where new vessel formation supports tumor growth. No studies have evaluated adropin in tumor-bearing models.

Immunogenicity: As a foreign peptide (despite the 100 percent sequence identity with endogenous adropin, the route and quantity of administration differ from physiological production), repeated exogenous administration could elicit anti-drug antibody formation, though no immunogenicity data have been reported.

11.3 Human safety data

No human safety data from interventional studies exist. The observational literature reports no adverse events associated with endogenous adropin levels (which are measured, not administered). Safety characterization in humans is entirely absent and represents a prerequisite for any future clinical development.

11.4 Reproductive and developmental safety

No reproductive or developmental toxicity data exist for adropin. Endogenous adropin is detected in human colostrum and breast milk, suggesting a physiological role in neonatal nutrition or metabolism [11]. The implications for exogenous administration in pregnancy or lactation are unknown.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five metabolic-regulatory peptide candidates against adropin, evaluated against five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The five candidates were selected as the principal circulating peptides with substantive research programs in metabolic, cardiovascular, or energy homeostasis regulation and with partial overlap in the biological space occupied by adropin.

12.1 Irisin (FNDC5 cleavage product)

Mechanism: Irisin is a 112-amino-acid myokine cleaved from the transmembrane protein fibronectin type III domain-containing protein 5 (FNDC5) in response to exercise and PGC-1alpha activation. It promotes thermogenesis by inducing browning of white adipose tissue through upregulation of uncoupling protein 1 (UCP1), with additional effects on glucose uptake, lipid metabolism, and bone remodeling [33].

Novelty: Moderate. Irisin was identified in 2012 by Bostrom et al. and generated substantial initial excitement as an "exercise hormone" [33]. The mechanism (white-to-brown fat conversion) was novel at the time of discovery but has been extensively characterized.

Effect size: Preclinical effect sizes on energy expenditure and adiposity are moderate. Human data are complicated by ELISA assay controversies regarding the specificity of commercial irisin antibodies, with some investigators questioning whether measured circulating irisin levels reflect the genuine peptide [34]. Exercise consistently increases circulating irisin, but the magnitude of metabolic benefit in human intervention studies has been modest.

Promising potential: Moderate. Irisin is not in clinical development as a therapeutic agent. Research interest remains active, with the compound serving as a biomarker of exercise-induced metabolic adaptation.

Side-effect profile: No adverse effects reported in preclinical studies; no human interventional data.

Overall validation: Moderate. Extensive preclinical literature, active biomarker research, but no clinical development trajectory.

Comparison to adropin: Irisin and adropin are both nutritionally and metabolically regulated peptides with overlapping downstream effects on glucose utilization and lipid metabolism. Irisin is exercise-responsive and acts primarily through adipose tissue browning, while adropin is diet-responsive and acts primarily through hepatic lipogenesis suppression, endothelial eNOS activation, and cardiac fuel switching. Adropin has stronger cardiovascular and neuroprotective data; irisin has stronger exercise-physiology positioning. Neither has human interventional data.

12.2 Fibroblast Growth Factor 21 (FGF21)

Mechanism: FGF21 is a 181-amino-acid hepatokine (also produced by adipose tissue, pancreas, and muscle) that signals through the FGFR1c-beta-klotho receptor complex to regulate glucose and lipid metabolism, insulin sensitivity, energy expenditure, and body weight [35].

Novelty: Low. FGF21 was identified as a metabolic regulator in 2005 and has been extensively characterized over two decades.

Effect size: Large in preclinical models; FGF21 analogs produce substantial weight loss and metabolic improvement in obese mice and nonhuman primates. In humans, the FGF21 analog pegozafermin (formerly BIO89-100) produced statistically significant reductions in hepatic fat fraction and improvements in metabolic parameters in Phase 2 trials for non-alcoholic steatohepatitis [36].

Promising potential: High. Multiple FGF21 analogs are in active clinical development: pegozafermin (89bio) is in Phase 3 for NASH; efruxifermin (Akerio Therapeutics) has reported positive Phase 2b results. FGF21 is the most clinically advanced metabolic peptide in this comparator panel.

Side-effect profile: FGF21 analogs have been generally well tolerated in clinical trials. Reported adverse events include nausea, diarrhea, and injection-site reactions. Bone loss has been observed in preclinical studies at supraphysiological doses.

Overall validation: High. Extensive preclinical and clinical evidence; multiple compounds in late-stage clinical development.

Comparison to adropin: FGF21 is substantially more clinically advanced than adropin, with established receptor pharmacology, human pharmacokinetic data, and late-phase clinical trials. Adropin's unique advantages are the endothelial-protective and neuroprotective mechanisms that FGF21 does not share. FGF21 has a clearer path to therapeutic application; adropin has a broader mechanistic portfolio but is at an earlier stage of characterization.

12.3 Growth Differentiation Factor 15 (GDF15)

Mechanism: GDF15 is a divergent member of the TGF-beta superfamily that signals through the GFRAL-RET receptor complex in the area postrema and nucleus of the solitary tract to suppress appetite and reduce body weight [37].

Novelty: Moderate. GDF15 was identified decades ago as a stress-responsive cytokine; its role as a weight-regulating hormone through GFRAL was characterized in 2017.

Effect size: Large in preclinical models for weight loss. Clinical development of GDF15-based therapies is ongoing but has been complicated by the association of elevated GDF15 with cachexia, cancer, and aging, raising questions about the desirability of sustained GDF15 elevation.

Promising potential: Moderate. Active clinical development by several companies, but safety concerns regarding chronic GDF15 elevation temper enthusiasm.

Side-effect profile: Nausea is the principal adverse effect, consistent with the area postrema mechanism. Long-term safety concerns regarding the association with aging and cachexia are unresolved.

Overall validation: Moderate. Strong mechanistic characterization; clinical development complicated by dual-edged biology.

Comparison to adropin: GDF15 and adropin act through entirely different receptor systems and biological mechanisms (appetite suppression versus metabolic fuel switching and endothelial protection). GDF15 is more clinically advanced but carries greater safety concerns. Adropin does not suppress appetite and does not share the cachexia association.

12.4 Apelin

Mechanism: Apelin is a family of peptides (apelin-13, apelin-17, apelin-36) derived from a 77-amino-acid precursor that signal through the APJ receptor (a class A GPCR) to modulate cardiovascular function, fluid homeostasis, angiogenesis, and glucose metabolism [38].

Novelty: Low to moderate. Apelin was identified in 1998; the research literature spans over two decades.

Effect size: Moderate in cardiovascular and metabolic preclinical models. Apelin produces vasodilation, positive inotropy, and glucose-lowering effects in animal models.

Promising potential: Moderate. Several apelin analogs are in early clinical development for heart failure and pulmonary arterial hypertension. The APJ receptor is a validated drug target.

Side-effect profile: Preclinical studies report hypotension at high doses; clinical safety data are limited to early-phase trials.

Overall validation: Moderate. Extensive preclinical literature; early clinical development.

Comparison to adropin: Apelin and adropin share cardiovascular-protective and metabolic-regulatory profiles but act through distinct receptors (APJ versus GPR19/VEGFR2). Apelin has more established receptor pharmacology and is further in clinical development. Adropin has stronger neuroprotective data and the unique eNOS-dependent stroke protection mechanism. The two peptides may be complementary research tools for cardiovascular and metabolic investigation.

12.5 MOTS-c (Mitochondrial Open Reading Frame of the 12S rRNA-c)

Mechanism: MOTS-c is a 16-amino-acid mitochondrial-derived peptide encoded within the mitochondrial 12S rRNA gene that regulates cellular metabolism through AMPK activation, affecting glucose uptake, fatty acid oxidation, and insulin sensitivity [39].

Novelty: High. MOTS-c was identified in 2015 by Lee et al. as the first mitochondrial-derived peptide with systemic hormonal activity, representing a conceptually novel class of metabolic regulators.

Effect size: Moderate in preclinical models. MOTS-c improves insulin sensitivity and prevents diet-induced obesity in mice. Effect sizes on glucose and lipid parameters are comparable to adropin in similar models.

Promising potential: Moderate. No clinical development as a therapeutic agent. Research interest is active, driven by the conceptual novelty of mitochondrial-encoded signaling peptides.

Side-effect profile: No adverse effects reported in preclinical studies. No human interventional data.

Overall validation: Low to moderate. Novel concept with emerging preclinical support; no clinical data.

Comparison to adropin: MOTS-c and adropin are both small metabolic peptides with insulin-sensitizing activity but are encoded by different genomes (mitochondrial versus nuclear), act through different receptors (AMPK activation versus GPR19/VEGFR2), and have distinct tissue expression patterns. MOTS-c has the conceptual novelty advantage; adropin has the larger research literature, stronger cardiovascular and neuroprotective data, and more extensive clinical biomarker characterization.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the metabolic peptide landscape. **Irisin** is the exercise-responsive myokine with overlapping metabolic effects but distinct mechanisms and no clinical development. **FGF21** is the most clinically advanced metabolic peptide in this panel, with late-phase trials and established receptor pharmacology, but lacks the endothelial and neuroprotective profile of adropin. **GDF15** is potent for weight regulation but carries safety concerns related to cachexia associations. **Apelin** shares cardiovascular-protective properties through a distinct receptor and is further in clinical development. **MOTS-c** offers conceptual novelty as a mitochondrial-derived peptide but has the least clinical characterization.

Adropin occupies a unique position in this landscape as the only compound with established preclinical evidence spanning metabolic regulation, endothelial protection, anti-atherosclerotic activity, and stroke neuroprotection through a unified eNOS-dependent mechanism. Its principal limitation is the absence of any human interventional data and the incomplete receptor pharmacology (GPR19 remains putatively rather than definitively assigned). Among the comparators, FGF21 is the clear leader in clinical translation; adropin's relative advantage is the breadth and coherence of its multi-organ pharmacology, particularly the neuroprotective profile that is unique in this comparator panel.

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