

RESEARCH MONOGRAPH . COMPOUND PROFILE

Humanin

A 24-amino-acid peptide encoded within the 16S rRNA of the mitochondrial genome, identified as a neuroprotective and metabolic factor with broad anti-apoptotic activity.

DOCUMENT	KDC-MN-1345
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AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	24-residue mitochondrial-derived peptide (MDP)

ABSTRACT

Humanin (Met-Ala-Pro-Arg-Gly-Phe-Ser-Cys-Leu-Leu-Leu-Leu-Thr-Ser-Glu-Ile-Asp-Leu-Pro-Val-Lys-Arg-Arg-Ala; molecular weight 2687.27 free peptide; CAS 330936-69-1) is a 24-residue peptide encoded within the 16S ribosomal RNA gene of the mitochondrial genome, identified by Yuichi Hashimoto and colleagues at Keio University in 2001 in a screen for anti-apoptotic factors that protected against amyloid-beta-induced neuronal death. Humanin is the founding member of the mitochondrial-derived peptide (MDP) family, a class of peptides encoded within mitochondrial DNA and translated from short open reading frames in mitochondrial RNAs; other family members include MOTS-c (KDC-MN-008), the SHLP family (small humanin-like peptides 1 through 6), and gau (gene antisense ubiquitous). The pharmacological signature of humanin includes anti-apoptotic activity through binding the BAX and BIM Bcl-2 family pro-apoptotic proteins, suppression of caspase activation, neuroprotection against amyloid-beta, prion peptide, and ALS-associated SOD1 toxicity in rodent and cell culture models, modulation of metabolic phenotypes (improved insulin sensitivity in rodent obesity models), and cytoprotection in models of myocardial ischemia and chemotherapy-induced toxicity. Receptors include the heterotrimeric ciliary neurotrophic factor (CNTF) receptor complex (CNTFR-WSX-1-gp130), the formyl peptide receptor 2 (FPR2), and direct cytoplasmic protein-protein interactions with BAX/BIM. The S14G analog of humanin (HNG; gly substituted for ser at position 14) is approximately 1000-fold more potent in neuroprotection assays and is the principal research-grade analog used in pharmacology studies. The

compound is research-grade with no regulatory approval; clinical development has been limited despite the strong preclinical signal, attributed in part to the narrow therapeutic window for neurodegenerative disease drugs and the sparse human pharmacokinetic characterization.

1. Compound Identification

Humanin is described as 24-residue mitochondrial-derived peptide (mdp). A 24-amino-acid peptide encoded within the 16S rRNA of the mitochondrial genome, identified as a neuroprotective and metabolic factor with broad anti-apoptotic activity.

1.1 Class summary

24-residue mitochondrial-derived peptide (MDP)

1.2 Subtitle

A 24-amino-acid peptide encoded within the 16S rRNA of the mitochondrial genome, identified as a neuroprotective and metabolic factor with broad anti-apoptotic activity.

2. Abstract

Humanin (Met-Ala-Pro-Arg-Gly-Phe-Ser-Cys-Leu-Leu-Leu-Leu-Thr-Ser-Glu-Ile-Asp-Leu-Pro-Val-Lys-Arg-Arg-Ala; molecular weight 2687.27 free peptide; CAS 330936-69-1) is a 24-residue peptide encoded within the 16S ribosomal RNA gene of the mitochondrial genome, identified by Yuichi Hashimoto and colleagues at Keio University in 2001 in a screen for anti-apoptotic factors that protected against amyloid-beta-induced neuronal death. Humanin is the founding member of the mitochondrial-derived peptide (MDP) family, a class of peptides encoded within mitochondrial DNA and translated from short open reading frames in mitochondrial RNAs; other family members include MOTS-c (KDC-MN-008), the SHLP family (small humanin-like peptides 1 through 6), and gau (gene antisense ubiquitous). The pharmacological signature of humanin includes anti-apoptotic activity through binding the BAX and BIM Bcl-2 family pro-apoptotic proteins, suppression of caspase activation, neuroprotection against amyloid-beta, prion peptide, and ALS-associated SOD1 toxicity in rodent and cell culture models, modulation of metabolic phenotypes (improved insulin sensitivity in rodent obesity models), and cytoprotection in models of myocardial ischemia and chemotherapy-induced toxicity. Receptors include the heterotrimeric ciliary neurotrophic factor (CNTF) receptor complex (CNTFR-WSX-1-gp130), the formyl peptide receptor 2 (FPR2), and direct cytoplasmic protein-protein interactions with BAX/BIM. The S14G analog of humanin (HNG; gly substituted for ser at position 14) is approximately 1000-fold more potent in neuroprotection assays and is the principal research-grade analog used in pharmacology studies. The compound is research-grade with no regulatory approval; clinical development has been limited despite the strong preclinical signal, attributed in part to the narrow therapeutic window for neurodegenerative disease drugs and the sparse human pharmacokinetic characterization.

3. Mechanism of Action

Anti-apoptotic through binding BAX and BIM. Receptor binding at CNTFR-WSX-1-gp130 trimer and FPR2. Suppression of caspase activation. Neuroprotection, metabolic improvement, and cytoprotection across multiple injury models.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Rodent and research-grade dosing 0.5 to 5 mg/kg intraperitoneal or subcutaneous. The S14G analog is used at proportionally lower doses.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Hashimoto Y, et al. A rescue factor abolishing neuronal cell death by a wide spectrum of familial Alzheimer's disease genes. Proc Natl Acad Sci USA 2001.
2. Cohen P, et al. Mitochondrially encoded peptides as a new class of metabolic regulators. Cell Metab 2014.
3. Lee C, et al. Humanin: a harbinger of mitochondrial-derived peptides. Trends Endocrinol Metab 2013.

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