

RESEARCH MONOGRAPH · COMPOUND PROFILE

KPV

A 3-amino-acid tripeptide derived from the C-terminus of alpha-MSH, characterized for anti-inflammatory effects in colitis, dermatitis, and hepatic injury models.

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ABSTRACT

KPV (sequence Lys-Pro-Val-OH; CAS 67727-97-3; molecular formula $C_{16}H_{30}N_4O_4$; molecular weight 342.43) is a synthetic tripeptide corresponding to residues 11-13 of alpha-melanocyte stimulating hormone (alpha-MSH), the C-terminal fragment that retains anti-inflammatory activity in many of the published preclinical models of acute and chronic inflammation. The tripeptide was originally characterized by Catania and Lipton in the early 1990s as part of a structure-activity relationship study of the alpha-MSH inflammatory pharmacology, with the goal of identifying a small fragment that retained the parent hormone's anti-inflammatory effects without the pigmentation, body temperature, and feeding-behavior effects mediated by the N-terminal portion of the hormone. KPV reproduced the anti-inflammatory effects of alpha-MSH in rodent models of acute lung injury, dextran sulfate sodium-induced colitis, contact dermatitis, and hepatic ischemia-reperfusion injury. The mechanism involves attenuation of NF-kappa-B activation, reduced pro-inflammatory cytokine production by activated immune cells, and modulation of the melanocortin system through receptors that are not yet fully characterized for the tripeptide fragment. There is no FDA-approved IND for KPV in any indication; preliminary clinical work has explored topical KPV preparations for ulcerative colitis and inflammatory dermatologic conditions. The compound is widely used in research-grade work on inflammation and tissue injury. The principal limitations on the strength of the evidence are the relatively small published literature compared to BPC-157 or TB-500 and the limited human pharmacokinetic data.

Compound identification

Nomenclature and synonyms

The compound is referred to as KPV, alpha-MSH(11-13), or as the C-terminal tripeptide of alpha-MSH. The CAS number is 67727-97-3. The PubChem CID is 95603. The compound is a small tripeptide and is sometimes listed in the literature without a formal compound code.

A point of nomenclature confusion is the relationship between KPV and the related tetrapeptide KPV-Asn (Lys-Pro-Val-Asn) and longer alpha-MSH fragments. Different research groups have studied different fragment lengths; the activity profiles vary with sequence length. Mass spectrometry identification of the supplied compound is essential.

Structural chemistry

The amino acid sequence is L-lysine - L-proline - L-valine, with a free N-terminal amine on the lysine and a free C-terminal carboxylate on the valine. The molecular formula is $C_{16}H_{30}N_4O_4$; the average molecular weight is 342.43 g/mol; the monoisotopic mass is 342.23 daltons. The peptide has no disulfide bridges, no aromatic residues, and no post-translational modifications.

The sequence is dominated by hydrophobic and basic character: the lysine epsilon-amine provides the major ionizable side chain, the proline contributes a constrained backbone, and the valine contributes hydrophobic character. The peptide carries a net positive charge of +1 at physiological pH. The isoelectric point is approximately 9.5.

Physicochemical properties

KPV is supplied as a white to off-white powder. The lot of record (Kodiac biolabs lot 20260110) conforms to this description. Solubility in water and bacteriostatic water is high; concentrations up to 10 mg/mL are routinely prepared without precipitation. The peptide is also soluble in 0.9 percent saline, PBS, and standard biological buffers. Solubility in DMSO is poor.

The peptide is stable in the lyophilized state at minus 20 degrees Celsius for at least 24 months. Reconstituted solutions in bacteriostatic water are stable at 2 to 8 degrees Celsius for at least 30 days. Freeze-thaw cycles should be avoided.

Discovery and developmental history

Origin in alpha-MSH structure-activity work

The anti-inflammatory effects of alpha-MSH were established in the 1980s through work characterizing the hormone's role in fever modulation, immune suppression, and tissue protection during acute injury. The 13-amino-acid full-length alpha-MSH (Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH₂) had inconvenient pharmacology for therapeutic development: the N-terminal portion drove pigmentation effects through MC1R, body temperature effects through MC3R/MC4R, and feeding-behavior effects through MC4R, while the anti-inflammatory effects appeared to localize to the C-terminal portion.

Anna Catania, James Lipton, and colleagues at the University of Texas Southwestern conducted a systematic structure-activity relationship study in the early 1990s and identified the C-terminal tripeptide KPV as the minimum sequence retaining anti-inflammatory activity in rodent fever and inflammation models. Subsequent work by the Catania and Lipton groups and by independent collaborators characterized KPV's effects in colitis, dermatitis, hepatic injury, and other inflammatory models.

Clinical translation

KPV has been studied in early-stage clinical work primarily for inflammatory dermatologic and gastrointestinal conditions. A small Phase 2 trial of topical KPV cream for atopic dermatitis was reported in the early 2010s with favorable preliminary results. Oral KPV has been evaluated in ulcerative colitis and inflammatory bowel disease in pilot studies. None of these programs has progressed to Phase 3 or regulatory approval. The compound is not a regulated drug substance in the United States, the European Union, or Japan.

Mechanism of action

Anti-inflammatory NF-kappa-B modulation

The most-cited mechanism is attenuation of NF-kappa-B activation in immune cells exposed to inflammatory stimuli. KPV reduces TNF-alpha and IL-6 production by LPS-stimulated macrophages, reduces neutrophil infiltration in tissue injury models, and attenuates the magnitude of the cytokine cascade in acute inflammation. The mechanism appears to involve direct inhibition of NF-kappa-B nuclear translocation, possibly through interference with IKK kinase activity or through stabilization of the I-kappa-B inhibitor.

Melanocortin receptor activity

The relationship between KPV and the melanocortin receptor family (MC1R, MC3R, MC4R, MC5R) is incompletely characterized. The full-length alpha-MSH activates all five melanocortin receptors with varying affinity; the tripeptide KPV does not appear to engage MC1R or MC4R at typical concentrations. Whether KPV's anti-inflammatory effects are mediated through MC3R, through MC5R, through a yet-uncharacterized receptor, or through direct intracellular effects is not fully resolved.

Tissue protection in colitis models

The most-cited downstream effect is protection in dextran sulfate sodium (DSS) and TNBS-induced colitis models. KPV administration in these models reduces histological damage scores, attenuates pro-inflammatory cytokine production in colonic tissue, and accelerates re-epithelialization of damaged colonic mucosa. The mechanism involves both the NF-kappa-B effects and direct effects on intestinal epithelial cell migration and proliferation.

Dermatologic effects

In contact dermatitis and atopic dermatitis models, topical KPV reduces inflammatory cell infiltration, attenuates pruritus-related behavior in animal models, and accelerates resolution of the dermatologic lesion. The mechanism involves both ef-

fects on resident skin immune cells (macrophages, dendritic cells, mast cells) and on keratinocyte cytokine production.

Limits of the mechanistic model

The mechanistic literature is solid for the anti-inflammatory phenotype but incomplete for the upstream initiating event. The receptor through which KPV acts is not definitively identified; multiple proposals (MC3R, MC5R, intracellular targets) are in circulation. The effects are reproducible across multiple laboratories but the dose-response relationships vary substantially across models. Investigators should treat the published results as indicative of an anti-inflammatory pharmacology with incompletely characterized molecular targets.

Pharmacokinetics

Routes of administration

Subcutaneous, intramuscular, oral, intracolonic (enema), and topical administration have been characterized in published preclinical work. Oral bioavailability is moderate; the small size of the tripeptide and the proline content provide partial protection against gastric peptidases. Intracolonic administration in colitis models bypasses gastric degradation and concentrates the peptide at the site of inflammation. Topical formulations have been developed for dermatologic indications.

Plasma half-life and tissue distribution

The plasma half-life is short, on the order of minutes, due to rapid peptidase clearance. Tissue distribution is broad following systemic administration. The relevant duration of biological effect is on the order of hours, reflecting persistence of downstream signaling effects after the parent compound has cleared.

Metabolism and excretion

KPV is rapidly hydrolyzed by serum and tissue peptidases, primarily at the central proline-valine bond. Major metabolites include the dipeptide Lys-Pro and the free amino acids; biological activity of these metabolites is not extensively characterized. Renal excretion of intact peptide and short fragments is the primary clearance route. The compound is not a known inducer or inhibitor of major CYP isoforms.

Reported research dose ranges

The published preclinical literature reports rodent doses ranging from 50 micrograms to 5 milligrams per kilogram by various routes, with most pharmacology studies clustering around 250 micrograms to 1 milligram per kilogram daily. Allometric scaling places the equivalent human exposure in the range of 36 micrograms to 700 micrograms per kilogram per dose, or approximately 2.5 to 50 milligrams per dose for a 70 kg subject.

The dose range commonly cited in research-grade vendor literature (200 to 500 micrograms per research subject per day, parenterally, or 2 to 5 milligrams per dose orally) is broadly consistent with the lower-to-mid end of the allometrically scaled range. Topical preparations typically use KPV at 0.05 to 0.5 percent in cream or gel formulations. Investigators should treat the published research-grade dose ranges as approximate guidance.

Sourcing and quality verification

Synthesis route

KPV is produced by solid-phase peptide synthesis using Fmoc chemistry. The 3-residue length and the absence of unnatural amino acids make the synthesis straightforward at any scale. The principal synthetic concerns are correct stereochemistry of the L-amino acids, complete deprotection, and adequate desalting to remove TFA counterions.

The lot of record (Kodiak biolabs lot 20260110) was synthesized by the supplier of record and shipped in lyophilized acetate salt form. The vendor analytical report records 99.40 percent purity by HPLC.

Common adulterants and impurities

The research-grade KPV supply chain has documented patterns of substandard product. Reported issues include:

1. Substitution of the longer alpha-MSH(11-14) tetrapeptide (KPV-Asn) or other related fragments. Mass spectrometry resolves these readily.
2. Racemization at the central proline during prolonged synthesis at elevated temperature. Chiral HPLC is required to detect this.
3. Excess acetate or trifluoroacetate counterions inflating apparent mass by 10 to 15 percent (proportionally significant because the parent peptide is small).
4. Endotoxin contamination from non-pyrogen-controlled synthesis.
5. Free amino acid contamination from incomplete cleavage cycles.

Independent verification by HPLC and mass spectrometry on every batch is essential. The vendor COA is necessary but not sufficient. Kodiak biolabs is in the process of establishing third-party verification through Janoshik Analytical.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous TFA (0.1 percent) to acetonitrile, monitoring at 215 nm, is the standard purity assay. The peptide does not absorb significantly above 220 nm due to the absence of aromatic residues; this complicates some standard quantification approaches and requires careful baseline correction. Identity confirmation by LC-MS yields a protonated molecular ion at 343.2 m/z.

Reconstitution and handling

Solvent system

KPV dissolves readily in water, bacteriostatic water, and 0.9 percent saline. The standard reconstitution protocol uses bacteriostatic water for any solution intended for storage beyond a single use. For acute experiments, sterile water for injection or PBS works. DMSO is not the appropriate vehicle.

Reconstitution protocol

A 5 mg vial reconstituted in 2 mL produces a 2.5 mg/mL solution; in 1 mL produces a 5 mg/mL solution. Allow the vial to rest at room temperature for 30 to 60 seconds, then gently swirl until the powder fully dissolves. The peptide is highly soluble; full dissolution is typically complete within 30 seconds.

Storage stability

Lyophilized KPV in the unopened vial: stable at minus 20 degrees Celsius for at least 24 months. Reconstituted solutions: stable at 2 to 8 degrees Celsius for at least 30 days. Aliquot working solutions to avoid freeze-thaw cycles.

Stack interaction considerations

KPV is occasionally combined with BPC-157 in research-grade gut protection protocols on the rationale that BPC-157's mucosal protection complements KPV's anti-inflammatory effects on colonic immune cells. The mechanistic case is plausible but not formally established in controlled comparison studies; investigators should treat the stack as additive rather than synergistic absent specific experimental evidence.

Combination with topical glucocorticoids in dermatologic preparations has been studied in pilot work on the rationale that KPV may permit lower glucocorticoid doses by augmenting the anti-inflammatory response. Combination with the regenerative peptide family (TB-500) is reported in research-grade tissue injury protocols.

Pharmacokinetic interactions with CYP-substrate compounds are not expected. KPV has no documented receptor-level interactions with conventional small-molecule pharmacotherapy.

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