

RESEARCH MONOGRAPH · COMPOUND PROFILE

Semax

A 7-residue peptide derived from ACTH(4-10), developed at the Russian Academy of Sciences and registered for clinical use in stroke recovery and cognitive indications.

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ABSTRACT

Semax (sequence Met-Glu-His-Phe-Pro-Gly-Pro; CAS 80714-61-0; molecular formula C₃₇H₅₁N₉O₁₀S; molecular weight 813.92) is a synthetic heptapeptide developed in the early 1980s at the Institute of Molecular Genetics of the Russian Academy of Sciences. The peptide is a stabilized analog of the N-terminal heptapeptide of adrenocorticotrophic hormone (ACTH(4-10)), a fragment that retains many of the cognitive and neuroprotective effects of the parent hormone without the steroidogenic effects mediated by the C-terminal portion. Semax extends the ACTH(4-10) sequence with the C-terminal tripeptide Pro-Gly-Pro (the same stabilizing extension used in Selank) to confer protection against rapid peptidase degradation. The compound is registered as a prescription medicine in the Russian Federation for ischemic stroke recovery, transient ischemic attack, and several other neurological and cognitive indications. The published preclinical and clinical record includes work on neuroprotection in cerebral ischemia models, modulation of BDNF and NGF expression, melanocortin receptor signaling effects, and cognitive enhancement endpoints. The compound is not approved by any regulatory authority outside the Russian Federation. The principal limitations on the strength of the evidence are the dominance of the Russian-language literature, limited Western independent replication of the most-cited findings, and the relatively small clinical sample sizes by Western regulatory standards. The lot of record at Kodiak biolabs (lot 20260331) carries a vendor-reported HPLC purity of 99.75 percent.

Compound identification

Nomenclature and synonyms

The compound is referred to as Semax. The original developmental designations include MEHFPGP, ACTH(4-7) Pro-Gly-Pro, and Russian transliterations of the ACTH analog terminology. The CAS number is 80714-61-0. The PubChem CID is 124819. The compound is registered in the Russian Federation under the trade name Semax.

Note: the Kodiak COA library data lists a corrected molecular weight of 813.92 (versus 888.92 stated on the supplier's COA). The corrected value is consistent with the published reference value for the heptapeptide MEHFPGP and is used throughout this monograph.

Structural chemistry

The amino acid sequence is L-methionine - L-glutamic acid - L-histidine - L-phenylalanine - L-proline - L-glycine - L-proline. The peptide is 7 residues. The N-terminal MEHF tetrapeptide corresponds to residues 4-7 of native ACTH and provides the receptor-binding pharmacophore; the C-terminal Pro-Gly-Pro tripeptide is the stabilizing extension common to both Semax and Selank.

The molecular formula is C₃₇H₅₁N₉O₁₀S; the average molecular weight is 813.92 g/mol; the monoisotopic mass is 813.36 daltons. The peptide has one methionine (oxidation-sensitive), no disulfide bridges, two prolines providing backbone constraint, and no post-translational modifications.

The N-terminal methionine, the central histidine, and the glutamic acid at position 2 provide the principal ionizable side chains. The peptide carries a mild net negative charge at physiological pH due to the glutamate carboxylate, partially balanced by the histidine imidazole; the isoelectric point is approximately 5.3.

Physicochemical properties

Semax is supplied as a white to off-white lyophilized powder. The lot of record (Kodiac biolabs lot 20260331) conforms to this description. Solubility in water and bacteriostatic water is high; concentrations up to 5 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 under standard light protection. The single methionine is oxidation-sensitive; prolonged exposure to atmospheric oxygen at elevated temperature can produce methionine sulfoxide impurities. 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 the Russian Academy of Sciences

Semax emerged from a research program at the Institute of Molecular Genetics of the Russian Academy of Sciences in the early 1980s. The starting point was the recognition that ACTH(4-10), the N-terminal heptapeptide of native adrenocorticotrophic hormone, retained many of the cognitive and neuroprotective effects of the parent hormone without the corticosteroid-stimulating effects mediated by the C-terminal portion. Like the related compound Selank (which targets anxiety rather than cognition), Semax was designed to extend the parent fragment's biological half-life by appending the stabilizing C-terminal Pro-Gly-Pro tripeptide.

The developmental work was led by Igor Ashmarin, Lyudmila Andreeva, Andrey Myasoedov, and colleagues. The compound was disclosed in Russian-language pharmacology literature in the late 1980s and progressed through clinical evaluation in the Russian Federation during the 1990s, culminating in registration as a prescription medicine for ischemic stroke and transient ischemic attack.

Clinical translation

Semax is registered in the Russian Federation for ischemic stroke recovery (within the acute and subacute window), transient ischemic attack, optic nerve atrophy, and several cognitive indications. The clinical record includes Phase 2 and Phase 3 trials for ischemic stroke with reported reductions in functional disability scores at 30 and 90 days post-stroke. Additional clinical work has explored Semax in attention-deficit conditions, in the treatment of cognitive deficits associated with chronic cerebrovascular insufficiency, and in optic neuropathies.

There is no FDA-approved IND for Semax in any indication. The compound is not a regulated drug substance in the United States, the European Union, or Japan. The Russian regulatory record does not directly translate to Western frameworks.

Mechanism of action

BDNF and NGF expression

The most-cited mechanism is upregulation of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) expression in hippocampus, cortex, and other CNS regions. The mechanism involves both direct effects on neuronal gene expression (mediated through signaling pathways downstream of melanocortin receptors) and indirect effects through modulation of the stress-response and neurotrophic gene expression program. The functional consequence is increased synaptic plasticity, enhanced long-term potentiation, and improved performance on learning and memory tasks in rodent models.

Melanocortin receptor signaling

Semax's parent compound ACTH is a master regulator of the melanocortin system. Semax retains some affinity for the melanocortin receptors, particularly MC4R, but the receptor-binding profile differs from native ACTH because the C-terminal portion of ACTH (which contributes to MC2R binding and corticosteroid stimulation) is absent. The functional consequence is melanocortin receptor activation that produces the cognitive and neuroprotective effects without the corticosteroid release.

Neuroprotection in ischemic injury

In cerebral ischemia models (middle cerebral artery occlusion in rodents), Semax administration during the acute and subacute phases reduces infarct volume, attenuates neurological deficit scores, and accelerates functional recovery. The mechanism involves both the BDNF/NGF effects and direct effects on cellular stress-response pathways including HSP70 induction, attenuation of NF-kappa-B activation, and modulation of microglial activation.

Enkephalinase inhibition

Like Selank, Semax has been reported to inhibit enkephalinase activity, producing accumulation of endogenous opioid peptides at synaptic sites. This mechanism may contribute to the analgesic effects reported in some preclinical studies and to the antidepressant-like effects in chronic stress models.

Cognitive enhancement

In healthy rodents and in models of age-related cognitive decline, Semax improves performance on attention, memory, and learning tasks. The magnitude of the effect varies across studies but is consistently positive in the published Russian-language literature. Western independent replication is sparse.

Limits of the mechanistic model

The mechanistic literature is dominated by Russian research groups. The BDNF and NGF effects are reproducible across multiple Russian laboratories and have been confirmed in some independent studies. The melanocortin receptor pharmacology is partially characterized. The direct cognitive enhancement claims are well documented in the Russian literature but limited in Western independent replication. Investigators should treat the published results as indicative of a neurotrophic and neuroprotective pharmacology with effect sizes that are consistent in the Russian literature but with limited independent confirmation.

Pharmacokinetics

Routes of administration

Intranasal administration is the standard route in Russian clinical practice and in the majority of preclinical work. The intranasal route bypasses gastric and first-pass hepatic degradation, achieves rapid systemic absorption, and provides direct access to the central nervous system through the olfactory and trigeminal pathways. Subcutaneous, intramuscular, and intravenous administration have been characterized in preclinical work; oral bioavailability is poor due to gastric peptidase degradation.

Plasma half-life and tissue distribution

Plasma half-life following intranasal administration is approximately 30 minutes. Brain penetration is documented through both olfactory pathway transport and trigeminal nerve transport, with peak brain concentrations reached within 30 to 60 minutes of intranasal dosing. The pharmacological effect duration extends substantially beyond the plasma half-life, on the order of hours to days for transcriptional effects on BDNF and NGF expression.

Metabolism and excretion

Semax is hydrolyzed by serum and tissue peptidases, with the C-terminal Pro-Gly-Pro tripeptide conferring substantial protection against the rapid degradation that limits the parent ACTH(4-10). Major metabolites include the central tetrapeptide MEHF and shorter fragments. Renal excretion of intact peptide and shorter fragments is the primary clearance route. The compound is not a known inducer or inhibitor of major CYP isoforms.

Reported research dose ranges

Russian clinical practice for ischemic stroke uses intranasal Semax at 1 percent solution (10 milligrams per milliliter), 2 to 3 milliliters per dose distributed across both nostrils, two to four times daily, for 5 to 10 day treatment courses. Allometric scaling of the rodent literature places the equivalent human exposure in this range.

The dose range commonly cited in research-grade vendor literature (1 to 3 milligrams per research subject, intranasally, two to three times per day, in 7 to 14 day cycles) is consistent with the clinical practice. Higher doses (up to 5 to 10 milligrams per dose) have been reported in some Russian clinical protocols for severe stroke. Investigators should treat the cycle-based dosing as central to the published pharmacology.

Sourcing and quality verification

Synthesis route

Semax is produced by solid-phase peptide synthesis using Fmoc chemistry. The 7-residue length is well within routine SPPS capacity. The principal synthetic concerns are coupling efficiency at the proline-rich C-terminal segment, oxidation of the N-terminal methionine during prolonged synthesis, and correct stereochemistry of all L-amino acids.

The lot of record (Kodiak biolabs lot 20260331) was synthesized by the supplier of record and shipped in lyophilized acetate salt form. The vendor analytical report records 99.75 percent purity by HPLC (vendor COA value) with a supplementary HPLC report at 99.76 percent. Note that the supplier's COA originally reported a molecular weight of 888.92, which is incorrect; the correct value of 813.92 has been verified independently and is the accepted reference value for the heptapeptide.

Common adulterants and impurities

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

1. Methionine sulfoxide formation at the N-terminal methionine, producing a peptide of mass +16 daltons relative to the parent. Mass spectrometry detects this readily; the oxidized impurity has reduced biological activity.
2. Substitution of Semax with the parent ACTH(4-10) heptapeptide (which is a different sequence) or with the related anxiolytic Selank. Mass spectrometry distinguishes these.
3. Deletion sequences from incomplete coupling at one of the prolines.
4. Racemization at the central histidine or phenylalanine during prolonged synthesis. Chiral HPLC is required to detect this.
5. Excess acetate or trifluoroacetate counterions inflating apparent mass by 8 to 12 percent.
6. Endotoxin contamination from non-pyrogen-controlled synthesis.

Independent verification by HPLC and mass spectrometry on every batch is essential, with particular attention to methionine oxidation status. 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 and 280 nm (the latter exploiting histidine and phenylalanine absorbance), is the standard purity assay. Identity confirmation by LC-MS yields a protonated molecular ion at 814.4 m/z. The acceptance criteria are: total purity above 98.0 percent at both wavelengths, identity confirmation within 0.5 ppm of theoretical mass, methionine sulfoxide impurity below 0.5 percent, and absence of major impurity peaks above 0.5 percent of the parent peak.

Reconstitution and handling

Solvent system

Semax dissolves readily in water, bacteriostatic water, and 0.9 percent saline. For intranasal use (the standard route in Russian clinical practice), the peptide is typically dissolved in 0.9 percent saline at 1 percent (10 milligrams per milliliter). For other routes, the standard reconstitution protocol uses bacteriostatic water for any solution intended for storage beyond a single use. DMSO is not the appropriate vehicle.

Reconstitution protocol

A 5 mg vial reconstituted in 0.5 mL produces the 1 percent (10 mg/mL) concentration commonly used for intranasal administration; in 2 mL produces 2.5 mg/mL. Allow the vial to rest at room temperature for 60 to 90 seconds, then gently swirl until the powder fully dissolves. The peptide is highly soluble; full dissolution is typically complete within 60 seconds.

Storage stability

Lyophilized Semax 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 and to limit methionine oxidation. Reconstituted nasal spray solutions should not be stored at room temperature beyond 24 hours.

Stack interaction considerations

Semax is occasionally combined with Selank in research-grade protocols on the rationale that the two peptides target overlapping but distinct CNS pathways (Semax for cognitive enhancement and stroke recovery, Selank for anxiety). The combination is documented in some Russian clinical practice but the formal synergy data are limited.

Combination with conventional cognitive-enhancement pharmacotherapy (acetylcholinesterase inhibitors, NMDA receptor modulators) is not specifically studied in formal clinical trials. The mechanism of Semax involves BDNF and NGF expression effects that may be complementary to acetylcholinesterase inhibition; investigators interested in the combination should generate experimental data in the model of interest rather than assuming synergy.

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

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This monograph is a research reference document. It does not constitute medical advice. The compound discussed is not approved by regulatory authorities outside the Russian Federation for any indication. Investigators are responsible for compliance with applicable laws and institutional review requirements in their jurisdiction.