

Semax

ACTH-derived neuroactive signalling and route-bound evidence

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Medical review

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ABSTRACT

Intranasal Semax changes BDNF/TrkB-associated biology in animals and produces acute measurable human connectivity effects.

This monograph evaluates Semax as the heptapeptide Met-Glu-His-Phe-Pro-Gly-Pro. It maps ACTH-derived identity, BDNF/TrkB biology, ischemia models and limited intranasal human neurophysiology without transferring those findings to injection.

This monograph begins with the molecule and follows the causal chain through biochemistry, cellular mechanism, exposure and integrated physiology. Population studies enter only at the terminal stress-test: useful for the proposition actually tested, incapable of defining the molecule or replacing the causal model.

ESTABLISHED	UNRESOLVED
• Exact heptapeptide sequence • BDNF/TrkB preclinical signals • Intranasal human neurophysiology	• Controlled contemporary efficacy • Injectable PK and outcomes • Long-term safety

EVIDENCE HIERARCHY

Mechanistic evidence is not a lower-grade substitute for population medicine. Physical constraints, biochemical measurements, historical and non-English records, exposure studies and clinical outcomes answer different questions. Controlled clinical trials test the complete implemented proposition; they cannot manufacture a missing identity, mechanism or exposure bridge.

I	Molecular identity and chemistry
II	Biochemistry and target architecture
III	Cells and ex-vivo tissues
IV	Animal and in-vivo pharmacology
V	Integrated physiology and translation
VI	Human PK and observational signal
VII	Controlled clinical trials

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ACTION LEDGER

Describe the action before judging its value.

Benefit is a downstream clinical judgement. The scientific object is the action itself: what moves, under which exposure, in which biological state, and where the inference stops.

01 Attributed biochemical action	Intranasal Semax changes BDNF/TrkB-associated biology in animals and produces acute measurable human connectivity effects.
02 Exposure and reachability	Human neurophysiological and clinical reports are predominantly intranasal. They cannot be transferred automatically to an injectable route.
03 Physiological direction is contextual	BDNF/TrkB signalling, neuroimmune transcription and network connectivity are state- and time-dependent. Their meaning differs between acute ischaemia, recovery, fatigue and an otherwise healthy brain. A neurophysiological response establishes that the system moved; durable cognition or neurological function requires a coherent downstream trajectory, not merely a larger biomarker signal.
04 Individual adjudication boundary	Human PK and independent trials connecting molecular or imaging target engagement to durable patient-important function. BDNF movement, transcriptomic change or fMRI connectivity does not by itself prove cognition enhancement, stroke recovery or systemic regeneration.

METHODS AND COVERAGE

A reproducible boundary, not an implied exhaustive review.

This curated mechanistic monograph uses primary indexed records and reference-chaining. It does not claim systematic-review completeness. Absence of a retrieved result is not evidence that an effect is absent.

SEARCH SURFACE	PubMed/MEDLINE primary records, Russian-language indexed abstracts, and reference-chaining for entity-defining, historical and translational studies. Language, geography, regulatory status and journal fashion are not evidence grades.
QUERY FRAME	Semax · ACTH(4-7) · Met-Glu-His-Phe-Pro-Gly-Pro · BDNF · TrkB · intranasal · stroke · functional connectivity
EVIDENCE CUTOFF	23 August 2026
ENTITY EXCLUSION	Semax is neither ACTH nor ‘Samax’. Intranasal evidence cannot establish injectable exposure, and an acute neural signal cannot be relabelled as clinical neuroprotection.
TRACEABILITY	12 extended claim units plus 2 historical records and 3 mechanistic-calculus records; 10 cited records in the complete corpus.
INTERPRETIVE RULE	Identity → physical constraint → measured reaction or binding → reachable exposure → system response → outcome. Statistical significance does not manufacture mechanism; mechanistic plausibility does not manufacture a patient outcome.

EVIDENCE ATLAS

Every claim keeps its experimental address.

12 claim units are mapped to evidentiary layer, experimental frame and source records. The layer describes the question answered; it is not a popularity score.

LAYER	EXPERIMENTAL FRAME	FINDING AND BOUNDARY	SOURCES
IMolecular identity	Molecular identity · claim 1	Semax is Met-Glu-His-Phe-Pro-Gly-Pro: an ACTH(4-7)-related tetrapeptide extended by Pro-Gly-Pro. It is not Samax, not ACTH, and not a mixture. The extension and absence of the full ACTH sequence are central to its distinct endocrine and neuroactive profile.	[1][2]
IMolecular identity	Molecular identity · claim 2	Most human work uses intranasal administration. Animal mechanistic studies also commonly use intranasal exposure. This creates a more coherent route chain than exists for injectable use, but human nasal PK and tissue exposure remain incompletely characterised.	[1][2][3]
IVIntegrated in-vivo model	BDNF and TrkB programme · claim 1	In rat hippocampus, a single intranasal dose increased BDNF protein, TrkB phosphorylation and selected BDNF and TrkB transcripts. The experiment also reported improved conditioned avoidance behaviour. This connects molecular signalling with a behavioural endpoint in the same species.	[1]
VIHuman exposure or signal	BDNF and TrkB programme · claim 2	Separate rat basal-forebrain work identified specific, reversible binding and increased BDNF after intranasal administration. These findings support a neurotrophic mechanism while leaving the proximal human molecular target and therapeutic exposure-response unresolved.	[4]
IVIntegrated in-vivo model	Ischemia and neuroimmune mechanisms · claim 1	Rodent focal-ischemia transcriptomics found that Semax changed immune-response, cytokine, stress-response and ribosomal gene programmes. The data suggest that neuroprotection, where present, may involve neuroimmune coordination rather than one isolated trophic pathway.	[5]
II/VMechanism and physiological translation	Ischemia and neuroimmune mechanisms · claim 2	An ischemia model creates a particular time-sensitive biological environment. Mechanisms observed after experimental occlusion cannot be assumed to improve cognition, fatigue or attention in a healthy brain.	[5]

LAYER	EXPERIMENTAL FRAME	FINDING AND BOUNDARY	SOURCES
VIHuman exposure or signal	Human neuroimaging · claim 1	A small resting-state fMRI study included 24 healthy participants, with 14 receiving intranasal Semax and 10 placebo. The investigators reported changes in the rostral default-mode-network subcomponent minutes after administration.	[2]
VIHuman exposure or signal	Human neuroimaging · claim 2	A larger connectomic experiment comparing Selank, Semax and placebo reported acute functional-connectivity changes involving amygdala-temporal networks. These are target-engagement-like neurophysiological signals, not direct evidence of memory improvement or stroke recovery.	[6]
IVIntegrated in-vivo model	Clinical stroke literature · claim 1	Historical clinical reports have described neurological signals when Semax was added in stroke care. Accessible reports are small, often incompletely described and embedded in treatment contexts that may not match modern reperfusion, imaging and rehabilitation standards.	[3]
IVIntegrated in-vivo model	Clinical stroke literature · claim 2	A contemporary claim requires a contemporary comparator. A signal against historical or non-equivalent care cannot define incremental benefit alongside current thrombolysis, thrombectomy, antithrombotic management and structured rehabilitation.	[3]
VIHuman exposure or signal	Translation boundary · claim 1	Semax has a defined molecule, biologically coherent preclinical evidence and measurable acute intranasal human neurophysiology. It lacks a mature, independently replicated clinical programme with route-specific PK, prespecified patient-important endpoints and long-term safety.	[1][2][3][6]
VIHuman exposure or signal	Translation boundary · claim 2	Imaging change, BDNF movement and transcriptomic response each demonstrate a level of biology. None alone establishes broad nootropic or neuroprotective efficacy. Injectable use would require a separate evidence chain beginning with exposure.	[1][2][5]

SECTION 01

Molecular dossier: the entity before the outcome

ENTITY — Met-Glu-His-Phe-Pro-Gly-Pro, an ACTH(4-7)-related heptapeptide

BIOCHEMICAL CLASS — Neuroactive melanocortin-derived peptide analogue

PRIMARY SYSTEM — BDNF/TrkB · neuroimmune transcription · acute network connectivity

IDENTITY BOUNDARY — Semax is neither ACTH nor ‘Samax’. Intranasal evidence cannot establish injectable exposure, and an acute neural signal cannot be relabelled as clinical neuroprotection.

SECTION 02

Historical and international corpus

Semax is a Soviet/Russian ACTH-fragment analogue studied since at least the late 1980s, with human stroke publications from the 1990s onward. It is not a century-old exact entity, but it has a much deeper translational history than a contemporary English-only review suggests.

The Russian corpus must be integrated with its original route, dose, treatment-era context and methods. Historical use is neither proof by longevity nor grounds for deletion.

SECTION 03

1989: ACTH(4-7)-PGP experimental programme predates modern indexing habits

A Russian primary experiment reported dose-specific effects of ACTH(4-7)-PGP on spatial learning. This establishes that the exact sequence lineage was under experimental study decades before recent transcriptomic and imaging papers.[7]

SECTION 04

1999-2001: Early Russian human neuroprotection programme

Clinical publications examined acute ischaemic stroke and post-hypoxic encephalopathy, including dose, neurological and electrophysiological observations. Their historical comparators and reporting standards limit modern effect estimation, but they are direct human evidence and must remain in the map.[8][9][10]

SECTION 05

Mechanistic calculus — CONSTRAINED: ACTH ancestry does not imply ACTH endocrine action

Semax retains a short ACTH-derived core and adds Pro-Gly-Pro but lacks the full hormone. Sequence relationship supports design provenance, not automatic melanocortin or adrenal equivalence.[1][7]

SECTION 06

Mechanistic calculus — MEASURED: Multiple molecular layers converge after nasal exposure

BDNF protein, TrkB phosphorylation, neuroimmune transcripts and acute connectivity changes have been measured in different systems. Convergence strengthens biological activity while leaving the proximal binding target incompletely resolved.[1][2][4][5][6]

SECTION 07

Mechanistic calculus — UNRESOLVED: Historical clinical signal needs a modern counterfactual

A treatment-era improvement cannot be transported unchanged into present stroke pathways. Contemporary reperfusion, imaging, rehabilitation and prespecified functional outcomes define a different causal comparison.[3][8][9][10]

SECTION 08

Causal architecture: ACTH ancestry does not define present pharmacology

Semax retains an ACTH(4-7)-related core and adds Pro-Gly-Pro, while lacking the full ACTH sequence. This architecture supports a distinct neuroactive profile and prevents automatic inheritance of ACTH endocrine effects.[1][2]

SECTION 09

Causal architecture: BDNF/TrkB is a developed mechanistic axis

Animal studies show BDNF protein movement, TrkB phosphorylation and associated transcript changes after intranasal exposure. These observations connect sequence, route and a neurotrophic signalling cascade.[1][4]

SECTION 10

Causal architecture: Ischaemia recruits neuroimmune networks

Experimental focal ischaemia produces Semax-associated changes in cytokine, immune-response and stress programmes. Such a time-sensitive injury environment cannot be equated with fatigue, attention or cognition in a non-ischaemic brain.[5]

SECTION 11

Causal architecture: Human imaging is target-engagement-like evidence

Acute connectivity changes after intranasal administration demonstrate a neural response under the studied conditions. They locate a biological effect but do not establish magnitude, persistence or patient benefit.[2][6]

SECTION 12

Molecular identity and entity resolution

Semax is the defined heptapeptide Met-Glu-His-Phe-Pro-Gly-Pro, derived from an ACTH(4-7) motif with a Pro-Gly-Pro extension. It is not 'Samax' and it is not a combination.

SECTION 13

Biochemical mechanism and target architecture

Preclinical studies report BDNF/TrkB and neuroplasticity-related changes. Network or molecular modulation is target engagement, not proof of cognitive or clinical benefit.

SECTION 14

In-vivo pharmacology and exposure

Human neurophysiological and clinical reports are predominantly intranasal. They cannot be transferred automatically to an injectable route.

SECTION 15

Integrated physiology and individual terrain

BDNF/TrkB signalling, neuroimmune transcription and network connectivity are state- and time-dependent. Their meaning differs between acute ischaemia, recovery, fatigue and an otherwise healthy brain. A neurophysiological response establishes that the system moved; durable cognition or neurological function requires a coherent downstream trajectory, not merely a larger biomarker signal.

SECTION 16

Terminal human stress-test

A small resting-state fMRI study included 24 healthy participants and reported network-level change. Small or methodologically limited stroke cohorts have reported clinical signals in treatment contexts that require comparison with modern stroke care.

SECTION 17

Counterevidence and causal boundaries

Imaging change does not establish cognitive benefit, and historical non-equivalent controls do not support a universal neuroprotection claim. Long-term and injectable safety remain unresolved.

SECTION 18

Scientific conclusion

Semax has defined molecular identity, biologically coherent preclinical evidence and limited intranasal human signals. Route, endpoint and contemporary comparator define what may be inferred.

SECTION 19

Molecular identity

Semax is Met-Glu-His-Phe-Pro-Gly-Pro: an ACTH(4-7)-related tetrapeptide extended by Pro-Gly-Pro. It is not Samax, not ACTH, and not a mixture. The extension and absence of the full ACTH sequence are central to its distinct endocrine and neuroactive profile.[1][2]

Most human work uses intranasal administration. Animal mechanistic studies also commonly use intranasal exposure. This creates a more coherent route chain than exists for injectable use, but human nasal PK and tissue exposure remain incompletely characterised.[1][2][3]

SECTION 20

BDNF and TrkB programme

In rat hippocampus, a single intranasal dose increased BDNF protein, TrkB phosphorylation and selected BDNF and TrkB transcripts. The experiment also reported improved conditioned avoidance behaviour. This connects molecular signalling with a behavioural endpoint in the same species.[1]

Separate rat basal-forebrain work identified specific, reversible binding and increased BDNF after intranasal administration. These findings support a neurotrophic mechanism while leaving the proximal human molecular target and therapeutic exposure-response unresolved.[4]

SECTION 21

Ischemia and neuroimmune mechanisms

Rodent focal-ischemia transcriptomics found that Semax changed immune-response, cytokine, stress-response and ribosomal gene programmes. The data suggest that neuroprotection, where present, may involve neuroimmune coordination rather than one isolated trophic pathway.[5]

An ischemia model creates a particular time-sensitive biological environment. Mechanisms observed after experimental occlusion cannot be assumed to improve cognition, fatigue or attention in a healthy brain.[5]

SECTION 22

Human neuroimaging

A small resting-state fMRI study included 24 healthy participants, with 14 receiving intranasal Semax and 10 placebo. The investigators reported changes in the rostral default-mode-network subcomponent minutes after administration.[2]

A larger connectomic experiment comparing Selank, Semax and placebo reported acute functional-connectivity changes involving amygdala-temporal networks. These are target-engagement-like neurophysiological signals, not direct evidence of memory improvement or stroke recovery.[6]

SECTION 23

Clinical stroke literature

Historical clinical reports have described neurological signals when Semax was added in stroke care. Accessible reports are small, often incompletely described and embedded in treatment contexts that may not match modern reperfusion, imaging and rehabilitation standards.[3]

A contemporary claim requires a contemporary comparator. A signal against historical or non-equivalent care cannot define incremental benefit alongside current thrombolysis, thrombectomy, antithrombotic management and structured rehabilitation.[3]

SECTION 24

Translation boundary

Semax has a defined molecule, biologically coherent preclinical evidence and measurable acute intranasal human neurophysiology. It lacks a mature, independently replicated clinical programme with route-specific PK, prespecified patient-important endpoints and long-term safety.[1][2][3][6]

Imaging change, BDNF movement and transcriptomic response each demonstrate a level of biology. None alone establishes broad nootropic or neuroprotective efficacy. Injectable use would require a separate evidence chain beginning with exposure.[1][2][5]

SECTION 25

Falsification map

Failure to reproduce BDNF/TrkB movement with authenticated material would weaken the neurotrophic model.

No route-specific human exposure would undermine pharmacological interpretation of intranasal dosing.

Connectivity change without durable function would falsify imaging-as-clinical-benefit inference.

RESEARCH AGENDA

What would materially change the conclusion?

01 Human intranasal PK and tissue-exposure studies

02 Modern controlled stroke adjunct trials

03 Cognition trials with prespecified functional endpoints

04 Independent replication of imaging findings

05 Long-term nasal tolerability

06 Separate injectable PK before parenteral claims

CITED PRIMARY EVIDENCE CORPUS

10 source records

This corpus documents the claims made in this monograph; it is not presented as an exhaustive systematic-review search.

Dolotov et al. Brain Res. 2006;1117:54-60. · PMID 16996037

Gusev et al. Zh Nevrol Psikiatr. 2018;118:61-68. · PMID 29798983

Dmitrieva et al. Semax regulates immune-response genes during ischemic brain injury in rats. BMC Genomics. 2017. · PMID 28255762

Chepurnova et al. ACTH(4-7)-PGP and spatial learning in rats. Fiziol Zh SSSR. 1989. Russian-language primary study. · PMID 2548895

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Lebedeva et al. Bull Exp Biol Med. 2018;165:653-656. · PMID 30225715

Dolotov et al. Semax binding and BDNF increase in rat basal forebrain. J Neurochem. 2006. · PMID 16635254

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Skvortsova et al. Semax in acute hemispheric ischaemic stroke: clinical and electrophysiological study. Zh Nevrol Psikiatr. 2001. · PMID 11517472

AUTHORSHIP AND ACCOUNTABILITY

Valentine Wibowo performed the conceptualisation, evidence synthesis, scientific interpretation and drafting. dr. I Wayan Cahyadi Surya Distira Putra, MPH completed medical review and approved the publication. Internal medical review is not represented as independent journal peer review.

No new patient data or human research were undertaken. The author and reviewer declare no personal financial competing interests. Clinic Terrain and Klinik Pratama Cepat Sehat provide clinical services; that institutional relationship is disclosed.