Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Noopept

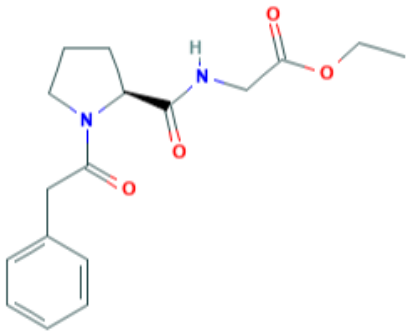
Evidence Summary

Although noopept is a purported cognitive-enhancing supplement, little clinical evidence supports its use.

Neuroprotective Benefit: Evidence in several mouse models suggests that noopept may be neuroprotective, but noopept has a very short half-life and some studies suggest that higher doses may not be beneficial. Also, almost all studies have been conducted in a single laboratory that used non-standard animal models and outcome measures.

Aging and related health concerns: Some evidence suggests that noopept may have beneficial metabolic effects, but its primary function is as a nootropic.

Safety: Noopept is associated with some mild side effects based on limited clinical evidence.

Availability: Not sold over the counter in the United States. Available with prescription in Russia	**Dose**: One clinical trial tested noopept at 10mg twice per day	**Molecular Formula:** $C_{17}H_{22}N_2O_4$ **Molecular weight:** 318.4 g/mol  **Source:** Pubchem
Half-life: ~5-10 minutes (rodents)	**BBB**: Penetrant (rodents)	
Clinical trials: 1 conducted, 0 ongoing	**Observational studies**: 0	

What is it?

Noopept (previously GVS-111) is a nootropic developed at the Zakusov Institute of Pharmacology (Russian Academy of Medical Sciences) by T. A. Gudasheva. It is one of several nootropics developed based on the structure of piracetam. Its advantage over piracetam is that it can be taken at a lower dose.

Noopept has a short half-life (~5-10 minutes – in rodents) and is not present in the brain one hour after administration. However, one of its metabolites, cycloprolylglycine (cPG) is increased in the brain one hour after noopept administration, and it is this metabolite that is thought to be responsible for noopept's longer-term nootropic activities (Gudasheva et al, 1997). cPG is also a metabolite of IGF-1 and is under development for rare neurological diseases by Neuren Pharmaceuticals.

Noopept is a popular cognitive-enhancing supplement in the nootropic community. Proposed mechanism of actions based on preclinical studies include increasing acetylcholine signaling, increasing the expression of BDNF and NGF, protecting from glutamate toxicity, and increasing inhibitory neurotransmission in the brain.

Neuroprotective benefit: Evidence in several mouse models suggests that noopept may be neuroprotective, but noopept has a very short half-life and some studies suggest that higher doses may not be beneficial.

Types of evidence:

- One open-label clinical study in patients with mild cognitive disorders
- Many preclinical studies for memory in mouse models

Human research to suggest prevention of dementia and cognitive aging

None

Clinical research to suggest benefits to patients with dementia or cognitive aging

In an open-label study of patients with mild cognitive disorders (e.g. cerebrovascular disease, post-traumatic CNS disorders), 56-day treatment with either noopept (10mg twice per day) or piracetam (400mgthree times per day) improved several aspects of mood and cognition (in noopept group, MMSE increased from 26 to 29). Possible side effects of noopept included sleep disturbances (5/31 patients), irritability (3/31), and increased blood pressure (7/31) (Neznamov and Teleshova, 2009).

Mechanisms of action from preclinical research

One study in rodents reported that noopept crossed the blood brain barrier. However, its half-life was only ~6 ½ minutes (Boiko et al, 2000).

In a rodent model of Alzheimer's disease (injection of Aβ into the Meynert basal nuclei – a model that reduces cholinergic neurons), 7-day treatment with noopept in both a preventative and treatment (15 days after Aβ injection) manner improved fear memory (Ostrovskaya et al, 2008). Noopept also improved memory in another model of Alzheimer's disease (olfactory bulbectomy) after 21 days of treatment (Ostrovskaya et al, 2007). Finally, noopept prevented the amnestic effects of cholinergic neurotransmission inhibitors (scopolamine and a nicotinic receptor antagonist) suggesting that one mechanism may be to boost cholinergic neurotransmission (Radionova et al, 2008; Belnik et al, 2007).

Acute administration of noopept slightly decreased neurotrophin factor (BDNF and NGF) expression in the cortex while increasing it in the hippocampus. Chronic (28-day) administration slightly increased BDNF in the cortex and increased both BDFN and NGF in the hippocampus (Ostrovskaya et al, 2008). Bel'nik et al (2009) tested the genotype differences of noopept administration in multiple mouse models on memory (Morris Water Maze). In a model (C57BL/6J) where memory was already good at baseline,

noopept administration had little effect. However, in a model (BALB/c) where memory was not as good at baseline, noopept increased memory retention. BALB/c mice are reported to have lower acetylcholine levels than C57BL mice, also suggesting that the effects of noopept may be through increased acetylcholine neurotransmission.

Ostrovskaya et al (2001) tested the anti-amnestic (i.e. memory enhancing) effect of different oral doses of noopept in an electric shock paradigm (animals were shocked in a dark component of a container and time spent in the dark container was measured afterwards). They found a two peak curve where doses of 0.5-0.7mg/kg enhanced memory, 1.2mg/kg did not enhance memory, and 10-20mg/kg enhanced memory.

In models of photothrombosis and compression-induced damage to the frontal cortex, daily treatment with noopept over 9 days improved fear memory (Romanova et al, 2002; Romanova et al, 2000).

In vitro studies

Noopept increased the viability of hippocampal neurons exposed to glutamate toxicity (Antipova et al, 2016), and improved the survival of neurons exposed to Aβ, reduced ptau, and increased the number of neurites (Ostrovskaya et al, 2014). In neuroblastoma cells expressing α-synuclein, noopept induced the sequestration of α-synuclein into amyloid fibrils, increased cell viability, and reduced oxidative stress (Jia et al, 2011).

Noopept may affect inhibitory activity in the brain. In hippocampal slices, application of noopept potentiated the inhibitor component of hippocampal neuron stimulation (Povarov et al, 2015; Kondratenko et al, 2010).

Cycloprolylglycine

Given noopept's short half-life, many of its cognitive-enhancing effects are likely mediated through its major metabolite cycloprolylglycine (cPG). cPG was reported to have an anxiolytic effect in rodent studies (Gudasheva et al, 2001), and administration of cPG enriched its concentration in the hippocampus more than the cortex (Boiko et al, 2010). In a model of intracerebral Aβ infusion, treatment with cPG over 14 days reduced hippocampal cell death, increased BDNF mRNA, and increased the expression of the anti-inflammatory cytokine IL-4 (but not IL-10) and reduced the expression of the pro-inflammatory cytokine IL-6 (but not IL-1β). It also increased mTOR phosphorylation. *In vitro*, cPG had no effect on survival of neurons exposed to Aβ but reduced the death of glial cells exposed to Aβ (Aguado-Llera et al, 2019).

In a model of global ischemic stroke, cPG improved neurological dysfunction after 3 days but not after 7 (by day 7, placebo treated rodents had improved to the same level as cPG treated rodents). *In vitro*, cPG protected hippocampal neurons from glutamate toxicity, though not at higher concentrations (Povarnina et al, 2015). cPG was also reported to increase the expression of BDNF in neuroblastoma cells and neurons exposed to glutamate toxicity (Gudasheva et al, 2016).

APOE4 Interactions:
None reported.

Aging and related health concerns: Some evidence suggests that noopept may have beneficial metabolic effects, but its primary function is as a nootropic.

Types of evidence:

- Several preclinical studies in diabetes and immune function

Diabetes:
In a diabetic prepubescent rat model (streptozotocin – STZ – injection), treatment with noopept reduced HOMA-IR and prevented the degeneration of hippocampal neurons, though it had no effect on cognitive performance (Gurbuz et al, 2019). In a mouse model of diabetes (STZ injection), both treatment with noopept starting 14 days before and after STZ injection reduced DNA damage in the pancreas, liver, and kidneys (Ostrovskaya et al, 2019). Noopept also stimulated the release of Glp-1, reduced insulin levels, and normalized glucose levels in a rat model of diabetes (STZ injection) (Ostrovskaya et al, 2014a; Ostrovskaya et al, 2014b; Ostrovskaya et al, 2013).

Immunity:
In mice, treatment with noopept increased the humoral immune response after administration of sheep erythrocytes and increased the proliferative activity of splenocytes. In addition, administration of noopept increased the phagocytic activity of peripheral macrophages (Kovalenko et al, 2007).

Safety: Noopept is associated with some mild side effects based on limited clinical evidence.

Types of evidence:

- One open-label clinical trial

One open-label study suggested noopept may be associated with sleep disturbances (5/31 patients), irritability (3/31), and increased blood pressure (7/31) in patients with mild cognitive disorders (Neznamov and Teleshova, 2009). Noocept is a common nootropic and is used in Russia, but there is little published human clinical evidence on its safety.

Drug interactions:
Since noopept is an unapproved nootropic with little clinical use, drug interactions are not known.

Sources and dosing:
Noopept is not sold over the counter in the United States. It is used clinically in Russia. The only clinical trial with results published in a peer-reviewed journal tested a dose of 10mg twice daily.

Research underway:
None reported

Search terms:
Noopept, cycloprolylglycine

Websites visited:

- Clinicaltrials.gov
- Pubmed
- Nootropic websites

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.