Pharmacological Cognitive Enhancement

Glutamatergic excitatory transmission as a target for drug development

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Introduction

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system and is known to play a critical role in normal cognitive functioning by interacting with its receptors: metabotropic and ionotropic, including NMDA, AMPA and kainate receptors. Currently the scope of scientific research is aimed to these last ones, as they present a promising potential to treat cognitive impairment due to its role in promoting memory formation in a process known as long-term potentiation (LTP).

LTP precisely strengths particular synapses upholding the development of intricate neural networks, the most broadly accepted biological substrate of memory and complex thinking. Communication within and between cortical networks is mainly mediated by glutamatergic transmission, then pharmacological agents that potentiate glutamate action should provide a solid neurobiological base to the enhancement of cognition.

Cognitive enhancement

- Improvement of cognitive abilities in individuals (mentally impaired and healthy)
- Not a novel topic in society → + presence as technical breakthroughs come along
- Arduous task (no consensus measure and ambiguous definition)
- Based on the modulation of transient telencephalic networks

Aims and Methods

- Provide a comprehensive and concise view of the pharmacological agents that are able to ameliorate cognition by modulating glutamatergic transmission in the central nervous system
- Highlight the shared importance of the two aspects involved in smart drug development: Neurobiology and Bioethics

Stage	Description	Specifics
1	Literature search at Pubmed and ScienceDirect as well as everyday journals for general public's opinion	Main search terms: Pharmacological cognitive enhancement, Neuroenhancement and Glutamatergic transmission
2	Screening of the most accurate high-impact articles, with special interest in reviews	Main sources: Nature Reviews Neuroscience, Neuron, Science and Journal of Neuroscience
3	Selection of useful information and analysis of bibliography	Comprehensive reading and study of scientific literature
4	Periodical check-up of new publications	Recurrent research at online search engines

Table 1. Research methods used for the review.

Long-term potentiation

LTP stands for long-term potentiation, an activity-dependent synaptic plasticity mechanism in which synapses are strengthened by the generation of molecular and structural changes that may last long periods of time, eventually resulting in augmented efficacy of the neural connection.

In order to trigger LTP, two events must take place simultaneously:

NMDAR activation ↓ LTP

1. Depolarization of the postsynaptic neuron
2. Release of glutamate by the presynaptic neuron

In physiological conditions the first requirement is generally satisfied by previous glutamate activation of AMPA receptors, which produces an excitatory postsynaptic potential due to the generation of an inward sodium current. This positively risen potential will facilitate the evacuation of the magnesium ions that normally block the pore of the NMDA receptor, which combined with the binding of presynaptic-delivered glutamate at the same time will allow ions to flow through the channel, creating a strong net calcium inward current. These calcium ions will act has key intracellular messengers in an essential step for the LTP establishment phase.

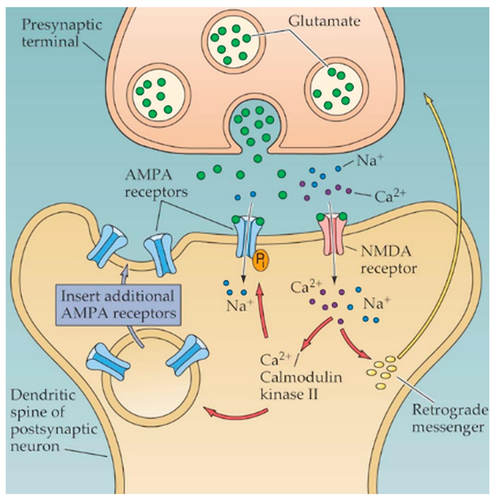


Figure 1. NMDA receptor-dependent LTP schematic. (wiki.bethanycrane.com)

Signaling pathway

- Kinases involved in AMPAR phosphorylation → + channel conductance
- Enzymes participating in vesicle trafficking → + postsynaptic receptor's density

Stimulation of genes → Protein synthesis → Maintenance of LTP

Pharmacological modulation of NMDAR activity

↑ Glycine
↑Neurosteroids
Antagonists

Direct modulation

↑NMDARs → ↑LTP → ↑L&M → **Cognitive enhancement**

↑AMPARs

Indirect modulation

Figure 2. Pharmacological modulation of NMDA receptor activity.

The NMDA receptor represents a prime target for cognitive enhancement given its critical role in LTP and cognitive processes. There exist multiple molecules that interact and influence NMDAR functionally, therefore providing a fruitful variety of targets to pursue enhancement. These substances can be classified in two groups: indirect modulators and direct modulators.

Indirect modulation

AMPAR activity lowers the threshold of NMDAR activation by bringing the resting potential of the postsynaptic neuron to more positive values, encouraging the opening of and promoting LTP. Consequently, AMPAR positive allosteric modulators hold great promises as cognitive enhancers. The most remarkable ones are ampakines, which are able to freely cross the blood-brain barrier and directly interact with AMPARs at the CNS, increasing excitatory transmission.

Mechanism of action

Ampakines enhance current flow by slowing receptor's dynamics (desensitization and deactivation), hence prolonging its open channel state. Remarkably, this effect only affects the receptors activated by endogenously released glutamate, therefore enhancing them in an activity-dependent manner, which combined with the absence of targets outside the CNS permits to obtain a positive modulation at a reduced dose hence avoiding the side effects that will produce excessive activation.

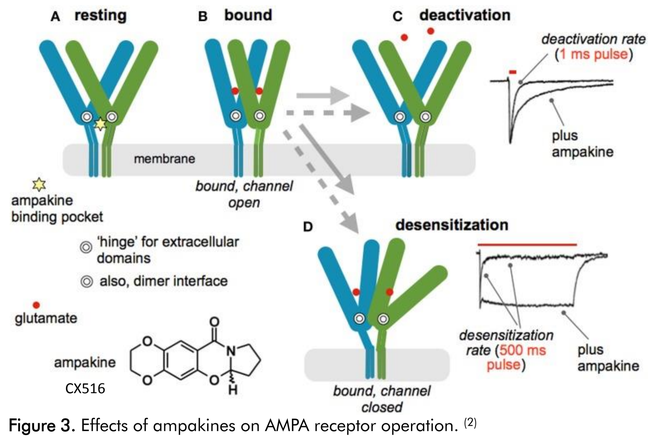


Figure 3. Effects of ampakines on AMPA receptor operation. (2)

Other beneficial effects

- Increased brain derived neurotrophic factor levels, which is known to chronically encourage induction and reinforce LTP consolidation.
- Enlarged cortical networks and increased nervous transmission for more complex computations.

Direct modulation

1. Glycine

Glycine (or D-serine) acts as an essential co-agonist of the NMDAR at glutamatergic synapses. Consequently, incrementing its levels augments the activity of NMDARs. This increase can be achieved by two methods:

- A) Inhibition of the high affinity glycine transporters that prevent its saturation in physiological conditions.
- B) Increase of D-serine extracellular levels by direct administration or inhibition of its catabolizing enzyme, D-amino acid oxidase.

2. Antagonists

Under certain conditions NMDAR antagonists can result in cognitive enhancement. This conception is based on the selective inhibition of pathological activation or excitotoxicity while preserving ordinary activation.

- C) The most prominent one is memantine, a drug used as treatment of Alzheimer's disease described as a fast, voltage-dependent ion pore channel blocker.
- D) It is also possible to increase extracellular magnesium concentration to resist receptor's overactivation.

3. Neurosteroids

E) Pregenenolone sulfate stands as the most promising neurosteroid for enhancement. After binding the extracellular component of NMDAR, the neurosteroid displays its intricate action as, even though the main outcome is potentiation, it can also weaken receptor's activity under certain conditions. The most recognized hypothesis consists in that its predominant facilitator role targets GluN2A/Glun2B subunit containing receptors whilst its inhibitory action is focused at GluN2C/GluN2C receptors.

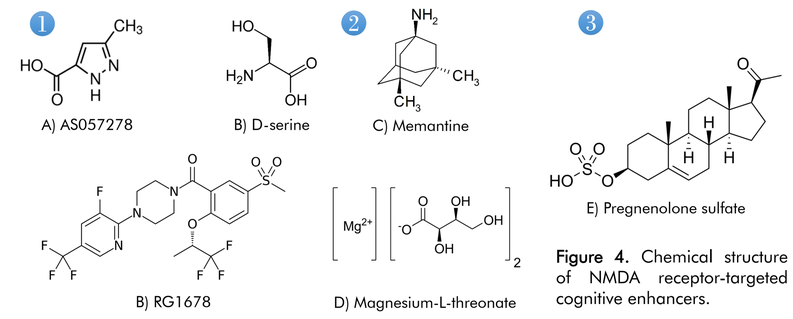
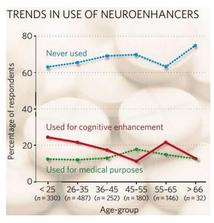


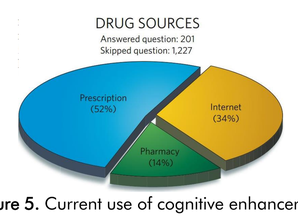
Figure 4. Chemical structure of NMDA receptor-targeted cognitive enhancers.

A problem of present day

Cognitive enhancer	Neuromodulatory mechanism	Cognitive functions improved	Currently recommended clinical use
Methylphenidate, amphetamine	Dopamine and noradrenaline reuptake inhibitors	Response inhibition, working memory, attention, vigilance	ADHD, wake-promoting agent
Caffeine	Non-selective adenosine receptor antagonist	Vigilance, working memory, incidental learning	–
Nicotine	Nicotinic cholinergic receptor agonist	Working memory, episodic memory, attention	–
Modafinil	Unknown, but effects on dopamine, noradrenaline and orexin systems proposed	Working memory, episodic memory, attention	Wake-promoting agent
Atomoxetine, reboxetine	Noradrenaline reuptake inhibitors	Response inhibition, working memory, attention	ADHD, depression
Donepezil, galantamine, rivastigmine (AChEI)	Blocks enzymatic breakdown of acetylcholine	Episodic memory, attention	Alzheimer's disease, PDD, DLB
Memantine	Noncompetitive, low-affinity, open channel blocker of the NMDA receptor	Episodic memory, attention	Alzheimer's disease

Table 2. Substances commonly used as cognitive enhancers.





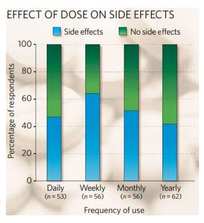


Figure 5. Current use of cognitive enhancers. (5)

At present day, relatively safe cognitive enhancers with moderate but clear effects in healthy individuals are available. The growing use of these substances has become relatively common among college students and also academia with strikingly high prevalence, consequently arising a series of ethical issues that concern both public opinion and normative debate. Should healthy individuals be able to use cognitive enhancers?

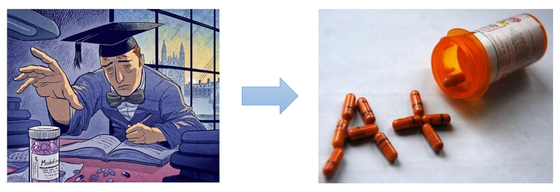
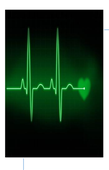


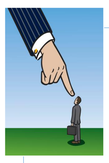
Figure 6. Cognitive enhancers are already a reality in academia.

Is it ethical?



Safety and Efficacy

- Modest positive effects
- Poor chronic administration data



Coercion

- Indirect (competition pressure)
- Direct (certain alertness demanding professions)

Fairness

- Equality of opportunity
- Honesty
- Authenticity

Lines of action

Reseach	Education
• Truthful quality information • Stimulate and fund new studies	• Universally understandable • Widely distributed
Use politics	**Legislation**
• Professional organizations • No ideological/political influences	• Novel legal framework • New organizations and regulatory entities

Figure 7. Ethical concerns and future pathway of cognitive enhancement.

Concluding remarks

- Cognitive enhancers have potential to improve life-quality of patients suffering impairments in mental functioning while also benefiting healthy individuals
- Like every technology, they can be used well or poorly. In order to use them consciously, further research is needed.
- The final beneficial outcome may probably outreach the risks.

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