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 strengthens 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 potentiating glutamate action should provide a solid neurobiological base to the cognitive enhancement.

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 telenaxonic networks

Long-term potentiation
LTP stands for long-term potentiation, an activity-dependent synaptic plasticity mechanism in which changes 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:
1. NMDAR activation
2. Release of glutamate by the presynaptic neuron

In physiological conditions the first requirement is generally satisfied by the previous glutamate activation of AMPA receptors, which produces an excitatory post synaptic 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-glutamate will at the same time allow ions to flow through the channel, creating a strong net calcium inward current. These calcium ions will act as key intracellular messengers in an essential step for the LTP establishment phase.

Pharmacological modulation of NMDAR 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 interest 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.

1. Glycine / Neurosteroids Antagonists

Indirect modulation
AMPA 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 amphetamines, which are able to freely cross the blood-brain barrier and directly interact with AMPARs at the CNS, changing 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.

Direct modulation
1. Glycine
Glycine (D- or D-serine) acts as an essential co-agonist of the NMDA at glutamatergic synapses. Consequently, increasing 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 catalyzing 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 excitation 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
Pharmacological modulation of ERG1687 stands as the most promising neurosteroid for enhancement. After binding the extracellular component of NMDAR, the neurosteroid displays its intrinsic action, as even 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 GluN2B/GluN2C receptors.

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 Biochemistry

A problem of present day
<table>
<thead>
<tr>
<th>Cognitive enhancers</th>
<th>Neurobehavioral mechanism</th>
<th>Current recommended dose</th>
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</thead>
<tbody>
<tr>
<td>Enhance choline transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improve dopamine release</td>
<td>Dopamine, noradrenaline, serotonin (reuptake inhibitors)</td>
<td></td>
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<tr>
<td>Improve GABA release</td>
<td>GABA, γ-aminobutyric acid (gabapentin, pregabalin)</td>
<td></td>
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<tr>
<td>Improve serotonergic release</td>
<td>Serotonin (indoleamine precursors, tryptophan, 5-HTP)</td>
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Safety and Efficacy
- Modest positive effects
- Poor chronic administration data

Coercion
- Indirect (competition pressure)
- Direct (certain apprehension)

Faithfulness
- Equality of opportunity
- Honesty
- Authenticity

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 outweigh the risks.

References

Concluding remarks