Final project

Universitat Autònoma de Barcelona

D-serine: The story of a gliotransmitter with an unexpected role in learning and memory

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BACKGROUND

There has been great interest in astrocytes since they were seen to modulate neuronal activity, as well as providing metabolic energy supply to neurons. Despite lacking electric excitability, astrocytes integrate information and release "gliotransmitters" into the synaptic cleft.

D-serine is a gliotransmitter which has recently been subject to extensive study, as increasing evidence shows that it plays an essential role in long-term potentiation (LTP), the cellular mechanism underlying learning and memory formation, by co-activating NMDARs. This was a role which was originally attributed to glycine.

NMDARs are synaptic glutamate receptors which are well-known for their role in long-term potentiation, though a slight fault in their regulation may lead to neurodegeneration or excitoxicity, often responsible for neuropathology.

AIMS

- To provide evidence of D-serine being responsible for modulating NMDAR-dependent synaptic plasticity by reviewing recent findings regarding the steps involved in its synthesis in the mammalian brain, its release from astroglia and its degradation
- To review studies that show effects of D-serine presence in the brain, both in health and disease, as well as pointing out limitations of these studies
- To discuss current and prospective approaches to development of therapeutic methods for treatment of illnesses and conditions caused, at least in part, by NMDAR-dysfunction

MAIN RESULTS

1) D-serine distribution throughout the brain:

Regionally: D-serine distribution mirrors that of NMDARs, glycine does not

→ D-serine is a more likely endogenous co-agonist of NMDAR

However, SR, the synthetic enzyme of D-serine, is found predominantly in neurons

2) The serine shuttle hypothesis

- The precursor of D-serine, L-serine, is produced within astrocytes from glucose
- L-serine is shuttled to neurons, where SR catalyses the production of D-serine from L-serine
- D-serine is shuttled back to astrocytes, from where it is released as a gliotransmitter

This shuttle between neurons and astrocytes allows D-serine to be produced in sufficient levels for gliotransmission, while avoiding SR elimination activity

3) NMDAR-mediated LTP depends on D-serine

NMDAR activation → LTP

D-serine is released from astrocytes via Ca^{2+}-dependent vesicular exocytosis. Once in the synaptic cleft, it can co-activate neuronal NMDAR and regulate LTP

Selective disruption of Ca^{2+}-dependent exocytosis → suppression of LTP at thousands of nearby synapses

→ D-serine → LTP

This is also observed in the SON during lactation → astrocytes enseathement of glutaminergic synapses is reduced during lactation → less availability of D-serine at synapse → local LTP

4) The D-serine pathway is highly regulated

- SR requires many co-factors to function correctly, such as Mg·ATP
- Vesicular release of D-serine from the astrocyte is induced by activation of non-NMDAR glutamate receptors, such as AMPARs, and requires Ca^{2+} signalling mechanisms
- Degradation of D-serine can take place by the enzyme DAAO, or by SR itself, which is a bifunctional enzyme, able to degrade both L- and D-serine to form pyruvate and NH_3
- NMDARs require binding of both glutamate and D-serine (or glycine, depending on regional availability), as well as post-synaptic depolarization to remove Mg^{2+} channel block, in order to function

Such tight regulation highlights the importance of D-serine has in the brain

The tripartite synapse: Astrocytes cover areas containing 300-600 dendrites, and closely interact with both pre- and post-synaptic neurons at multiple synaptic sites

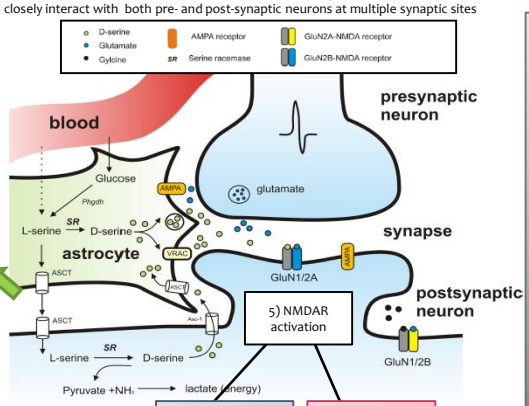

Figure courtesy of Van Horn et al., 2013

Physiological conditions

- Promotion of protein synthesis involved in initial phases of LTP

Pathological conditions

Hyperfunction

- Overactivation of the NMDAR may be caused by excessive levels of D-serine, either because of excessive synthesis by SR or by under-regulated degradation by DAAO
- Related illnesses and conditions: Alzheimer's disease and cerebral ischemia

Hypofunction

- Hypofunction of the NMDAR may be due to low availability of D-serine, either because of low synthesis rate or excessive degradation
- The most common and most studied illness related with this NMDAR-dysfunction is Schizophrenia

Whether caused by excessively high or insufficient levels of D-serine, unbalanced activation of NMDARs leads to neuropathology

7) Therapeutic prospects

- All neurologic diseases may, in some way, be related with homeostatic dysfunction. Therefore, dues to astrocytes' known role in metabolic regulation, cause of neurologic disease can usually be trailed back to astrocytes
- However, due to recent evidence of astrocytes and their gliotransmitters in higher brain functions, it is now necessary to study these molecules in full detail
- Knowledge of the D-serine pathway is useful for development of new therapeutic agents for treatment of illnesses and conditions related with impaired learning and memory
- SR can be used as a therapeutic target to help achieve adequate levels of D-serine:
  - Inhibiting SR catalytic activity or enhancing its elimination activity will help reduce D-serine levels
  - Inhibiting SR elimination activity or enhancing its catalytic activity will help increase D-serine levels
- DAAO, D-serine degradatory enzyme, is also a potential target to help balance D-serine levels
- Exogenous D-serine can also be administrated. This has already been seen to enhance effect of antipsychotics for treatment of schizophrenia

Further study of the D-serine pathway will provide promising insights for prospective development of therapeutic agents. However, potential side effects must also be taken into consideration.

Abbreviations: AMPAR: α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionaten receptor; $Ca2+$: calcium ions; DAAO: D-amino acid oxidase; LTP: long-term potentiation; $Mg2+$: magnesium ions; NMDAR: N-methyl-D-aspartate receptor; SR: serine racemase

CONCLUSIONS

- Since their discovery, understanding of astrocytes and how they contribute to brain function has radically changed. Astrocytes are now acknowledged as key participants in brain functions such as learning and memory formation, which they modulate by releasing gliotransmitters into the synaptic cleft.
- D-serine is an essential gliotransmitter for synaptic plasticity, as it is the primary endogenous co-agonist of the NMDAR. Therefore, it has a role in learning and memory, functions that were traditionally believed to depend solely on neurons.
- Due to the importance of the D-serine pathway, it is highly regulated at all stages, from D-serine synthesis to its release and levels of available D-serine are strictly regulated in order to maintain adequate levels for functional NMDAR activation.
- Errors occurring during regulation of D-serine result in pathological consequences, as unbalanced activation of NMDARs, whether by excessive or insufficient activation, is a potential cause of illnesses and conditions related with impaired learning and memory
- Due to the tight relation between D-serine and neuropathology has lead to extensive study of the D-serine pathway in order to develop new therapeutic techniques.
- Further study of D-serine, among other gliotransmitters, and factors involved in its regulation, will be both useful and necessary to take a step nearer towards full understanding of brain function, and also to provide information for therapy development.

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