BACKGROUND

There has been great interest in astrocytes since they were seen to modulate neuronal activity, as well as providing metabolic energy to neurons. Despite lacking electric excitability, astrocytes integrate information and release neurotransmitters into the synaptic cleft. D-serine is a neurotransmitter 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 role 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 excitotoxicity, 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 stages involved in its synthesis in the mammalian brain, its release from astroglial 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:
   - D-serine is an excitatory amino acid co-agonist of NMDA receptors. It has been shown that D-serine can support the transmission of glutamatergic signals, even when NMDA receptors are blocked.
   - D-serine is produced and released by astrocytes, indicating a role in the regulation of synaptic plasticity.

2) The serine shuttle hypothesis
   - Evidence indicates that D-serine is released from astrocytes and shuttled to neurons, where it can modulate excitatory neurotransmission. This shuttle between astrocytes and neurons allows for the regulation of synaptic transmission.

3) NMDAR-mediated LTP depends on D-serine
   - NMDAR activation requires the presence of glutamate and D-serine for potentiation.
   - D-serine is released from astrocytes to support NMDAR activation.

4) The D-serine pathway is highly regulated
   - Regulation of D-serine levels is critical for synaptic plasticity.
   - Factors such as transcriptional activity and metabolic processes modulate D-serine availability.

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 NMDA receptor. Therefore, it has a role in learning and memory functions, which 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 excessive or insufficient activation, is a potential cause of illnesses and conditions related with impaired learning and memory.
- Due to the tight regulation between D-serine and neuropathology, it has become essential to study its role in the pathophysiology of neuropsychiatric disorders.

REFERENCES