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D-Serine as a Modulator in the Nervous System

Ferdinand Hucho*

D-Amino acids occur rarely in nature. The genetic process only has codes, which consist of nucleotide triplets, for the 20 "standard" L-amino acids. On the other hand, D-amino acids do exist in the cell wall of gram negative bacteria, in numerous peptide antibiotics, and in other natural systems. Unlike the L-amino acids, they are not taken up with food or synthesized stereospecifically. They are formed by racemization from their L congeners, a process which is enzymatically catalyzed by racemases.

Unexpectedly, two Japanese laboratories reported some time ago the existence of D-serine and D-aspartate in mammals as well, in the brains of rats and humans.[12] Over the years, evidence accumulated for the fact that D-serine in mammalian brains is not an artefact, but is, rather, an important signalling molecule.[3] This hypothesis was recently strengthened by the findings of Snyder's group at the Johns Hopkins University in Baltimore.[4] They succeeded in cloning and sequencing a serine racemase from a mammalian brain. This protein represents a novel enzyme, possibly a first member of a whole family of enzymes, without any significant homology to other known amino acid racemases from lower organisms (with the exception of a short consensus sequence forming the binding site for pyridoxal phosphate). The enzyme is 339 amino acids long, has a calculated relative molecular mass of 36.3 kDa, and operates with the coenzyme pyridoxal phosphate (Figure 1).

Several amino acids, such as L-glutamate, glycine, and γ-aminobutyric acid (GABA) serve in the nervous system as neurotransmitters by transmitting nerve impulses from cell to cell. D-Serine does not seem to be such a transmitter, but rather a "neuromodulator", an essential regulator at synapses which use L-glutamate as an excitatory transmitter. D-Serine is not released from neurons, like a "normal" transmitter, but from astrocytes, a type of glia cells. In these cells Snyder and his co-workers localized the serine racemase.

To appreciate this discovery one has to take a closer look at the neurochemistry of glutamatergic synapses. L-Glutamate is the most important excitatory transmitter in the central nervous system (CNS) of vertebrates. (Insects use L-glutamate peripherally, that is, at their nerve – muscle synapses.) L-Glutamate is released presynaptically and triggers an effect postsynaptically, after it has bound to receptor proteins. Glutamate receptors comprise a large and complex group of

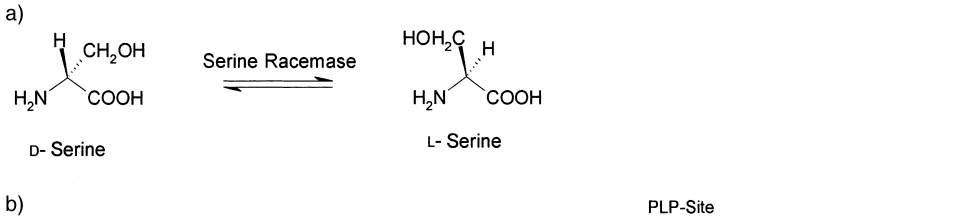

Figure 1. a) The reaction catalyzed by serine racemase. b) The amino acid sequence of serine racemase (single letter codes). The binding site for the coenzyme pyridoxal phosphate, close to the N terminus, is underlined.

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receptors.[5] For our purpose primarily one subtype of these is of interest, the so-called NMDA receptors.[6] NMDA stands for *N*-methyl-D-aspartate, a nonnatural molecule which activates specifically this subtype of glutamate receptors. NMDA receptors are of special interest because they play a key role in the CNS with processes involved in learning and memory, with the regulation of growth and programmed death (apoptosis) of neurons, but also with pathological phenomena like strokes, hypoxia, ischemia, neurodegenerative diseases, epilepsy, and schizophrenia.

NMDA receptors are "ligand-gated ion channels": after binding the neurotransmitter (L-glutamate) the receptor protein forms a cation-selective channel in the postsynaptic membrane, through which primarily calcium ions diffuse into the cell. Interestingly, L-glutamate alone is insufficient for activation of this ion channel. Electrophysiologists observed long ago that glycine is required as a coactivator.[7] Besides the binding site for L-glutamate the receptor protein contains another site for glycine. (This site was recently localized by recombinant DNA techniques in the primary structure of the receptor.[8]) From the very beginning it was not really clear whether glycine or another molecule functions as the physiological coactivator in vivo. Johnson and Ascher, who discovered the glycine effect,[7] speculated that the glycine concentration in the brain is sufficiently high to saturate the glycine binding sites. Others questioned this and postulated either the existence of another endogenous ligand or a locally upregulated glycine concentration. Now, D-serine could be the hypothetical endogenous ligand for the coactivator site.

This interpretation is supported by several experimental results. D-Serine is able to replace glycine in the experimental system; it is about three times as powerful as glycine. With serine-specific antibodies, Snyder and co-workers were able to show that there is a close correlation between the concentrations of D-serine and NMDA receptors in mammalian brains.[3] Removal of D-serine by means of a D-amino acid oxidase reduces the possibility of activating the NMDA receptor considerably. D-Serine occurs in high concentrations in astrocytes; its release from which can be triggered by glutamate and specific ligands of the other members of the receptor family, the so-called non-NMDA receptors. The last, the most important piece of the puzzle is the proof that a serine racemase exists in those astrocytes.

The picture is now complete (Figure 2). Normally, excitatory impulse transmission goes through non-NMDA receptors. Only with very strong, long-lasting excitation, such as with considerable presynaptic release of L-glutamate, are the NMDA receptors activated too. As soon as the released glutamate secures it from neighboring astrocytes, the coactivator D-serine is supplied. The activation of the NMDA receptors then has the consequences listed above.

However, the physiological function of this coactivation remains unclear. The NMDA receptor is regulated by a variety of mechanisms. For example, its ion channel is blocked by a magnesium ion. This block is released when a second nerve impulse arrives at a neighboring synapse of the same cell, resulting in a depolarisation of the membrane. This too is a "coactivation", in this case by a second nerve impulse. This mechanism makes sense when two nerve impulses have to be coordinated, for example, in the case of associative learning. A comparable "purpose" still has to be found for the coactivation by D-serine.

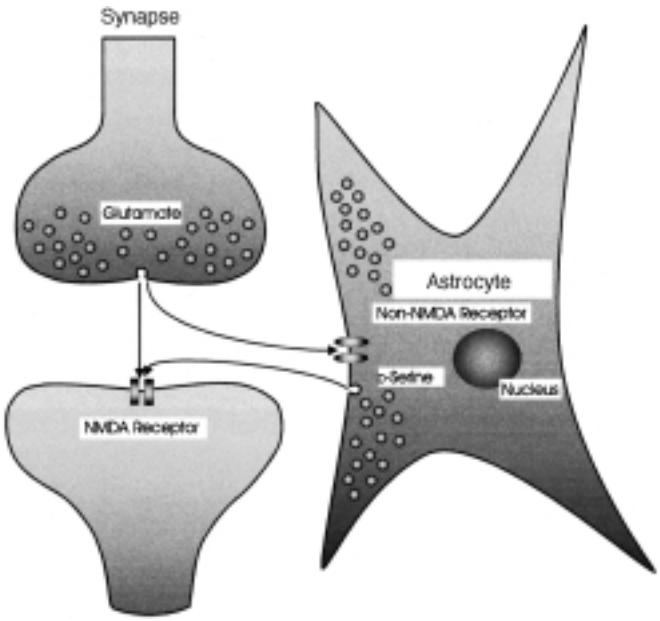

Figure 2. Schematic representation of a glutamatergic synapse, consisting of a nerve ending (top) with its glutamate-containing vesicles and the postsynaptic cell (below) with its NMDA receptors. (The non-NMDA receptors, which are also present here, have been omitted to simplify the figure. The vesicular exocytosis of D-serine from astrocytes and the D-serine uptake system have not yet been shown experimentally.) Next to the synapse, an astrocyte is depicted; this cooperates with the synapse in multiple ways. Amongst others, non-NMDA receptors are found here which regulate D-serine exocytosis after activation by L-glutamate. Only with this D-serine can the NMDA receptors of the postsynaptic cell be activated.

Already, the discovery of the neuromodulatory effect of D-serine is of great practical importance. By considering the medical implications of the NMDA receptors, novel drug targets can now be envisaged. Inhibitors of NMDA receptors and their ion channels are applied as neuroprotective agents against strokes, ischemia, and epilepsy, receptor activators are developed for schizophrenia. With D-serine known to be a NMDA-receptor regulator, new leads for novel targets are at hand. Possible drug targets are enzymes of serine metabolism (including the serine racemase), serine transporters, key proteins of D-serine exocytosis machinery, or the D-serine binding site on the receptor itself.

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