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Review

The role of D-serine in peripheral tissues

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ABSTRACT

A considerable level of D-serine (a free D-amino acid) was discovered, surprisingly, in the mammalian brain in the early 1990s. Since then, D-serine has been considered to be a co-agonist of glutamate at the glycine site of NMDA receptors. D-serine is synthetized by racemization of L-serine in most neural and non-neural cells, and modulates a variety of physiological functions in mammals. In addition to the central nervous system, NMDA receptors have an important function in the modulation of physiological processes in peripheral tissues. Thus, investigations on the functions of D-serine in the peripheral nervous system, as well as the visceral organs, have gained attention in recent years. In this review we summarize the current knowledge on the role of D-serine in the kidneys, skeletal system, skin as well as on the non-adrenergic, non-cholinergic transmission within the autonomic nervous system.

Contents

1. Introduction

Until 1992 it was believed that D-amino acids did not exist in substantial quantities in eukaryotes and that only L-amino acids were important for their function as protein building blocks and metabolic intermediates. However, after Hashimoto et al. (1992) discovered the presence of free D-serine in rat brain, the study of D-amino acids in the body acquired relevance for investigation. In 1999, Wolosker et al. purified a soluble enzyme from rat brain that catalyses the direct racemization of L-serine to D-serine (Wolosker et al., 1999). Further investigations showed that D-serine plays an important role in the central nervous system as an endogenous ligand for the glycine site of glutamate N-Methyl-D-Aspartate (NMDA) receptors (Mothet et al., 2000a, 2000b). Since then, the role of D-serine has been extensively studied in the central nervous system (Gundersen et al., 2015; Bardaweel et al., 2014). In

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addition to the central nervous system, NMDA receptors have an important function in the modulation of physiological processes in peripheral tissues (Gill and Pulido, 2001). Thus, investigations on the functions of D-serine in the peripheral nervous system, as well as the visceral organs, have gained attention in recent years. In this review we summarize the current knowledge on the role of D-serine in peripheral tissues.

1.1. Cell expression, synthesis and degradation of D-serine

D-Serine synthesis is attributed to Serine Racemase (SR), which catalyses the synthesis of D-serine from L-serine (Wolosker and Mori, 2012). SR is localized in different tissues of the central nervous system, as well as peripheral tissues (Xia et al., 2004). In the periphery, SR mRNA has been found in the heart, skeletal muscle, kidney, liver (Xia et al., 2004), lower oesophageal sphincter (Ghasemi-Kasman et al., 2012), corpus cavernosum (Ghasemi et al., 2010), chondrocytes (Takarada, et al., 2008), osteoblasts (Takarada et al., 2012) and skin (Inoue et al., 2014). In addition to performing the racemization reaction, Foltyn et al. (2005) found that SR is also involved in the elimination of D-Serine through α-β elimination activity, generating pyruvate and ammonia. D-serine metabolism is also regulated by allosteric modulators, such as ATP. Foltyn et al. (2005) found that ATP had moderate effects on the partitioning between racemization of L-serine and α-β elimination, favouring α-β elimination and stimulating its efficiency 10-fold. Previous experiments (De Miranda, et al. 2002) revealed that the complex Mg-ATP acts as a physiological co-factor that stimulates 5–10 times the rates of racemization and pyruvate production. In general, this data demonstrates the involvement of ATP in modulation of SR function.

In addition to modulation of D-serine level by SR, D-amino acid oxidase (DAAO) is another enzyme that can degrade D-serine in both the central nervous system as well as peripheral tissues. DAAO was first discovered in 1935 by Sir Hans Krebs (Krebs, 1935) whilst performing experiments on the metabolism of amino acids in porcine kidney. Western blot analysis of DAAO has shown high levels of DAAO protein in the cerebellum, however, no DAAO has been detected in the frontal cortex, hippocampus or striatum, suggesting that DAAO may regulate D-serine levels in the cerebellum only (Horio et al., 2011). DAAO protein was also found to be expressed at high concentrations in the kidney of wild type (WT) and SR knockout (SR-KO) mice (Horio et al., 2011), but was not detected in other tissues, such as the lower oesophageal sphincter (Ghasemi-Kasman et al., 2012), corpus cavernosum (Ghasemi et al., 2010), bone cells (Takarada et al., 2012) or mouse liver (Konno et al., 1997). Thus, both SR and DAAO play an important role in the regulation of D-serine concentration in tissues.

1.2. D-serine and human diseases

After D-serine was discovered in the rat brain (Hashimoto et al., 1992), further studies investigated its effects in the central nervous system. It was found that neural cells synthesize D-serine from L-serine through SR. SR is abundantly expressed in glial cells, but both neurons and glial cells are involved in D-serine synthesis (Ehmsen et al., 2013). Furthermore, studies revealed that brain D-serine is a physiological co-agonist of glutamate, almost as potent as glycine, which acts on the key neurotransmitter receptor NMDA for its full activation (Mothet et al., 2000a, 2000b). Had D-serine been discovered sooner in the mammalian brain, then the glycine site on the NMDA receptors would probably have been named 'D-serine site' instead. NMDA receptors are essential for excitatory synaptic transmission involved in physiological pathways, such as learning and memory, which are linked to long-term synaptic plasticity in the hippocampus caused by Long-Term Potentiation (LTP) (Wolosker, 2006). Yang et al. (2003) demonstrated that astrocyte-derived D-serine was required to induce LTP in an NMDA receptor-dependent manner.

NMDA receptor activity is highly regulated, since its over-activation leads to neurotoxicity, as seen in pathological conditions, such as stroke and neurodegenerative diseases (Kemp and McKernan, 2002). Experiments in rat brain cell cultures showed that neuronal D-serine accounts for a significant fraction of NMDA receptor-mediated neurotoxicity in addition to glia contribution with the production of growth factors and regulation of extracellular glycine levels (Kartvelishvily, et al. 2006).

Furthermore, D-serine may play a role in the pathophysiology of neuropsychiatric disorders, such as schizophrenia, which may be linked to NMDA receptor hypo-function (Wolosker et al., 2002). Studies in genetic and pharmacological animal models with decreased D-serine levels have shown that these animals displayed behavioural abnormalities similar to those seen in schizophrenia (Labrie et al., 2012). Moreover, exogenous administration of D-serine and related compounds improved several phenotypes relevant to schizophrenia, which could have positive clinical implications in humans (Labrie et al., 2012). Tsai, et al. (1998) performed a clinical trial in Taiwanese schizophrenic patients who received D-serine as adjuvant treatment. The results indicated that those patients who received D-serine treatment, improved positive, negative and cognitive symptoms seen in schizophrenia. In addition, this clinical trial showed that D-serine did not worsen side effects from other antipsychotics, which may be due to its selective action at the NMDA-glycine site. Therefore, D-serine could be considered as a therapeutic approach for schizophrenia, which is different from the dopaminergic approach. However, further clinical trials are required to confirm the efficacy of D-serine therapy. D-serine role in central nervous system disorders also involves chronic epilepsy, in which low D-serine levels may lead to a deficiency in NMDA receptor activation, synaptic plasticity and cognitive function. Thus, the administration of exogenous D-serine may normalise NMDA receptor function and treat cognitive dysfunction seen in epilepsy (Klatte et al., 2013). It has been shown that serum levels of serine enantiomers are higher in patients with depression (Hashimoto et al., 2015) and that D-serine levels are also higher in Alzheimer´s disease (Madeira et al., 2015). Therefore, D-serine has the potential to be used clinically as a novel biomarker or treatment for some neuropsychiatric disorders. Although the function of D-serine within the central nervous system has been studied extensively (Bardaweel et al., 2014), details of its role in peripheral organs remain to be uncovered. It is important, given the fact that SR is expressed in peripheral tissues. Thus, any intervention that involves elevation or inhibition of D-serine concentrations in the management of neuropsychiatric conditions, may have unwanted side effects on peripheral organs (e.g. nephrotoxicity). The focus of this review is on our current understanding of the role of D-serine in peripheral tissues.

2. D-serine concentration in the peripheral tissues

Apart from neural tissues, D-serine has been detected in plasma as well as peripheral organs. Horio et al. (2011), studied the contribution of SR in D-serine synthesis in peripheral tissues by comparing D-serine levels in SR-KO and WT mice. Their data showed that D-serine levels in the kidneys, testes and muscles were significantly lower in SR-KO mice compared to WT mice. Whereas, D-serine concentrations in the liver, spleen, pancreas, epididymis, heart, lungs and eyeballs did not differ from those found in SR-KO mice. In addition, serum levels of D-serine were not different between WT and SR-KO mice, suggesting that the presence of D-serine in the blood may not contribute to the