Animal Nutrition 4 (2018) 311–315

Contents lists available at ScienceDirect

Animal Nutrition

journal homepage: http://www.keaipublishing.com/en/journals/aninu/

Review Article

Role of D-aspartate on biosynthesis, racemization, and potential functions: A mini-review

Yuying Li [a, b], Hui Han [a, b], Jie Yin [a, b], Tiejun Li [a, c, *], Yulong Yin [a, c, *]

[a] Key Laboratory of Agro-Ecological Processes in Subtropical Region, National Engineering Laboratory for Pollution Control and Waste Utilization in Livestock and Poultry Production, Hunan Provincial Engineering Research Center for Healthy Livestock and Poultry Production, Scientific Observing and Experimental Station of Animal Nutrition and Feed Science in South-Central, Ministry of Agriculture, Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha 410125, China

[b] University of Chinese Academy of Sciences, Beijing 100039, China

[c] Hunan Co-Innovation Center of Animal Production Safety, Changsha 410128, China

ARTICLE INFO

Article history:
Received 9 October 2017
Received in revised form
20 March 2018
Accepted 3 April 2018
Available online 16 April 2018

Keywords:
D-aspartate
Biosynthesis
Racemization
Nutrition
Functions

ABSTRACT

D-aspartate, a natural and endogenous amino acid, widely exists in animal tissues and can be synthesized through aspartate racemase and transformed by D-aspartate oxidase (DDO). D-aspartate mainly serves as a neurotransmitter and has been demonstrated to exhibit various physiological functions, including nutritional potential, regulation on reproduction and hormone biology, and neuron protection. This article mainly reviews the synthesis, racemization, and physiological functions of D-aspartate with emphasis on the potential in diseases.

1. Introduction

Most amino acids include asymmetric-carbon atoms and exhibit 2 stereoisomers: left-handed (L-forms) and right-handed (D-forms) (Fig. 1) (Katane and Homma, 2011; Fujii et al., 2011), while only L-forms occupy the protein-building residues (Chung and Reed, 2015). Thus, some researchers speculated that only L-amino acids play functional roles in the body (Katane and Homma, 2011).

Aspartate widely exists in animal tissues with D-enantiomers, especially in nervous and reproductive systems (Ota et al., 2012; Di Fiore et al., 2014). In 1977, high concentration of D-aspartate has been firstly found in the brain of *Octopus vulgaris* Lam (D'Aniello and Giuditta, 1977) and D-aspartate in other tissues has been also detected subsequently, including heart, lung, stomach, intestine (Motoie et al., 2009), salivary glands (Masuda et al., 2003), seminal plasma and spermatozoa (D'Aniello et al., 2005), neural system (D'Aniello and Garcia-Fernàndez, 2006), knee cartilage (Fisher et al., 2006), testis (Lamanna et al., 2006), pre-ovulatory ovarian follicle (D'Aniello et al., 2007), and retinae (Opere et al., 2009). Wide existence of D-aspartate in body tissues suggests a potential physiological function in animals. Indeed, various studies focused on the regulatory effects of D-aspartate on the nervous (D'Aniello, 2007), endocrine, and reproduction (Lamanna et al., 2007). For example, D-aspartate contributes to the synthesis and release of glucocorticoids, prolactin, oxytocin, and steroids (D'Aniello et al., 2017). Currently, nutritional potential of D-aspartate has been investigated and the results found that low-dosage of D-aspartate improved growth performance and stress-resistance in animal industries. Here, we reviewed the biosynthesis, racemization and functional roles of D-aspartate in animals with emphasis on D-aspartate related signaling pathways.

* Corresponding authors.
E-mail addresses: tjli@isa.ac.cn (T. Li), yinyulong@isa.ac.cn (Y. Yin).

Peer review under responsibility of Chinese Association of Animal Science and Veterinary Medicine.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.aninu.2018.04.003

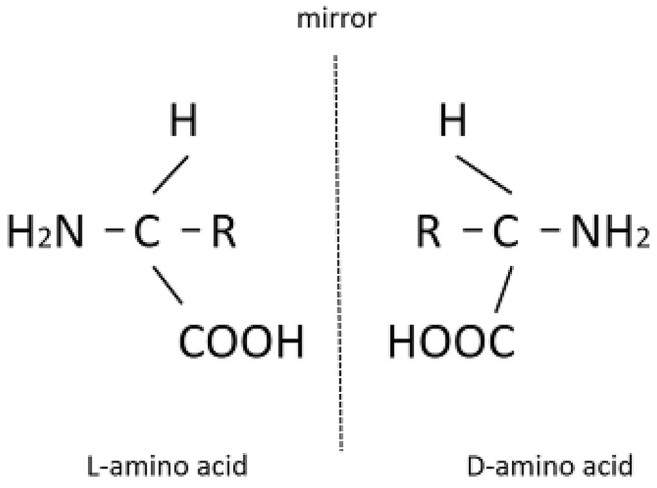

Fig. 1. D- and L-forms of amino acid (Chung and Reed, 2015).

2. D-aspartate in biosynthesis and racemization

D-aspartate can be synthesized in body tissues, which was firstly found in rat pheochromocytoma PC-12 cells (Koyama et al., 2005). In the body, D-aspartate racemase mainly contributes to the biosynthesis of D-aspartate by converting L-aspartate to D-aspartate (D'Aniello et al., 2011; Kim et al., 2010). Mouse glutamic-oxaloacetic transaminase 1-like 1 has been reported to encode Asp racemase and synthesize substantially D-aspartate from L-aspartate in adult neurogenesis (Tanaka-Hayashi et al., 2015; Kim et al., 2010; Matsuda et al., 2015). Synthesized D-aspartate can be oxidized by D-aspartate oxidase (DDO) and tissue D-aspartate concentration is mainly controlled by DDO activity, as DDO is the only enzyme known to selectively degrade D-aspartate (Van Veldhoven et al., 1991; D'Aniello et al., 1993; Cristino et al., 2015). For example, D-aspartate is abundant during the animal embryo and parturient of the brain and markedly reduced in the maturity due to the change of DDO activity (Punzo et al., 2016; Han et al., 2015). Furthermore, inhibition of DDO activity shows a sustained overflow of extracellular D-aspartate (Punzo et al., 2016). In $DDO^{-/-}$ mice (lacking *DDO* gene), the amounts of D-aspartate drastically increase compared with the wild-type mice ($DDO^{+/+}$) (Han et al., 2015).

3. Functions of D-aspartate

3.1. Potential nutrition

Lower-dosage D-aspartate improves growth performance, indicating a potential nutritional function in animal nutrition. For example, D-amino acid mixed with L-amino acid improve mouse growth performance, while excess D-amino acid inhibit growth (Berg, 1953). Similarly, oral administration of D-aspartate (0, 3.75, 7.5 and 15 mmol/kg body weight) linearly decreased feed intake (Erwan et al., 2013). Zhang et al. (2015) reported that excess D-aspartate acts as a potent damaging agent for DNA, vitamin C and E, and thus inhibits cell growth. The possible mechanism of D-aspartate in the body may be N-methyl-D-aspartate receptors (NMDAR) and L-Glu/L-aspartate transporter signals. D-aspartate can activate metabotropic glutamate receptors 5 (mGlu5) (Molinaro et al., 2010) and stimulate NMDAR-mediated neurotransmission by directly acting at the glutamate-binding site (*GluN1* and *GluN2B* subunits) of NMDAR, thus functioning as an endogenous agonist for this subclass of glutamate receptors (Errico et al., 2013; Cristino et al., 2015). Moreover, when intracellular uptake the D-aspartate, D-aspartate can be released by L-Glu/L-aspartate transporter that makes use of the Ca^{2+}-mediated manner after electrochemical stimulation (Savage et al., 2001; Muzzolini et al., 1997) and its uptake by Na^{+}/K^{+} electrical or chemical manner to against their concentration gradient (Adachi et al., 2004; Koyama et al., 2005; Errico et al., 2015). Therefore, we speculate that the proper dose of D-aspartate may play a potential value in nutrition and excess D-aspartate blocks the synthesis and metabolism of other important substances in the body.

3.2. D-aspartate in reproduction

D-aspartate has a positive effect on reproduction in animals by improving sperm quality, testosterone synthesis, spermatogenesis, and steroidogenesis proliferation (Fiore et al., 2017). For example, dietary 200 mg/kg per day BW D-aspartate can improve fresh and post-thawed sperm quality and post-thawed sperm fertility in male broiler breed, especially for sperm cryopreservation (Ansari et al., 2017). Giacone et al. (2017) reported that the effect of D-aspartate on reproduction may be due to the antioxidant function and protecting DNA integrity, which may further improve sperm motility and embryo development (Barbato et al., 2017). Santillo et al. (2016) also reported that D-aspartate activates proliferative pathways in GC-1 cells (mitotic germ cell). Meanwhile, D-aspartate in rats improves testosterone synthesis and activates testicular NMDAR, extracellular signal-regulated kinase (ERK) pathway, and androgen receptor (Santillo et al., 2014). Similarly, D-aspartate stimulates spermatogonia proliferation through the NMDAR-mediated ERK and ser-ine-threonine protein kinase (AKT) pathways (Palazzo et al., 2016), which further activates the P450 aromatase/ERb pathway (Santillo et al., 2016) (Fig. 2). D-aspartate also either stimulates steroidogenesis and spermatogenesis proliferation by binding to the NMDAR and thereby increasing the expression of the steroidogenic cascade enzymes by cAMP or stimulates mitogen-activated protein kinase (MAPK) and AKT pathways and then increased the expression of androgen receptor (Fig. 3) (Di Fiore et al., 2016).

3.3. Serving as endogenous neurotransmitter

D-aspartate is founded in the multitude brain regions (Palazzo et al., 2016), such as hippocampus and prefrontal. In mammals, D-aspartate is found in synaptic vesicles of nerve endings (D'Aniello et al., 2011) and maintains long-term potentiation and regulatory effect on the synaptic plasticity decay in the hippocampus of rodents (Errico et al., 2011a, 2011b). D-aspartate excites dopamine neurons and exerts a protective uptake mechanism by stimulating NMDA receptor and metabotropic glutamate receptors to prevent the neuronal degeneration (Krashia et al., 2016). Also, DDO with the change of D-aspartate concentration has been reported to regulate the homeostasis of glutamatergic system and, thus, suppresses neurodegenerative processes (Cristino et al., 2015). Moreover, D-aspartate plays important roles in plasticity, physiology, neuronal dendritic morphology, gray matter volume, and brain activity in mammals (Errico et al., 2014). For example, treatment with D-aspartate (20 mmol/L) in drinking water markedly alleviates mechanical allodynia through glutamate neurotransmission normalization after spared nerve injury in neuropathic mice (Palazzo et al., 2016).

3.4. Regulation of hormone release

D-aspartate plays an important role in the synthesis and release of hormones, such as glucocorticoids, prolactin, oxytocin, growth hormone (D'Aniello et al., 2000), and steroids in the prefrontal

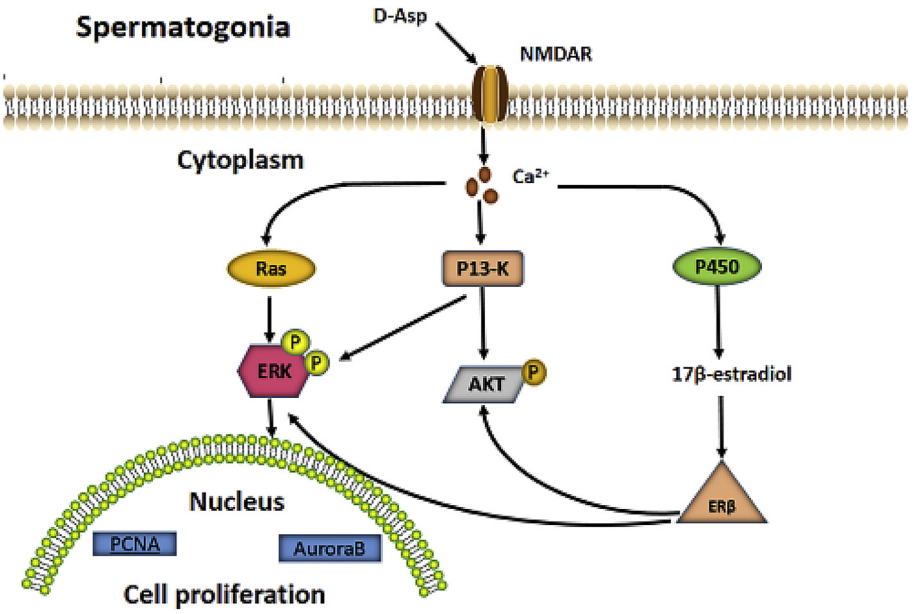

Fig. 2. Schematic representation of molecular pathways activated by D-aspartate in spermatogonia (Santillo et al., 2016). NMDAR = N-methyl-D-aspartate receptor; Ras = renin-angiotensin system; PI3-K = phosphatidylinositol-4,5-bisphosphate 3-kinase; ERK = extracellular signal-regulated kinase; AKT = serine-threonine kinase; ERβ = estrogen receptor β; PCNA = proliferation cell nuclear antigen.

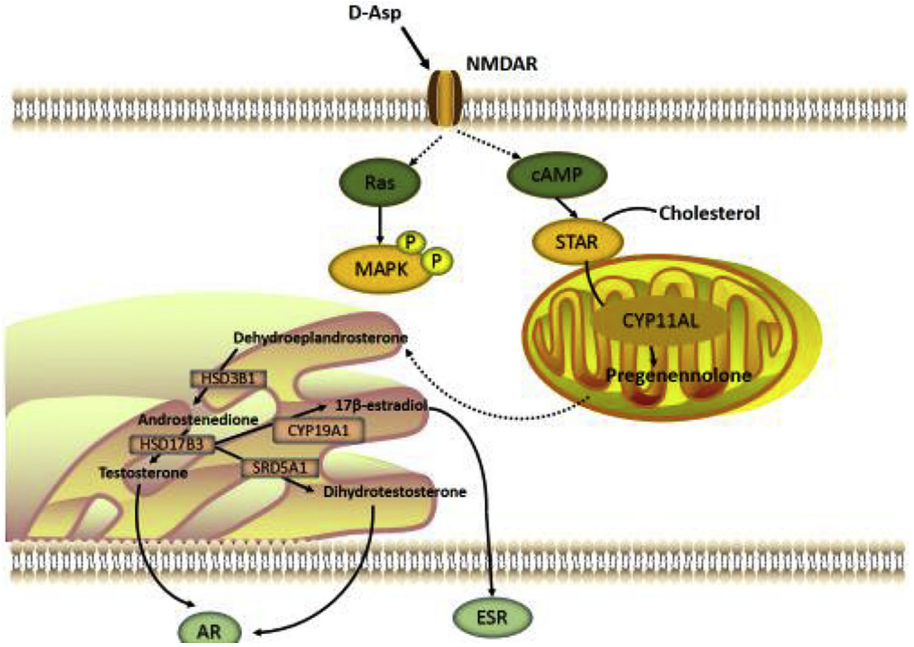

Fig. 3. Schematic representation of molecular pathways activated by D-aspartete in Leydig cell (Di Fiore et al., 2016). cAMP = cyclic adenosine monophosphate; MAPK = mitogen-activated protein kinase; STAR = steroidogenic acute regulatory protein; CYP11AL = P450 cholesterol side-chain cleavage; HSD3B1 = 3β-hydroxysteroid dehydrogenase; HSD17B3 = 17β-hydroxysteroid dehydrogenase; CYP19A1 = cytochrome P450 aromatase; SRD5A1 = 5α-reductase; AR = androgen receptor; ESR = estrogen receptor.

cortex and hippocampus (D'Aniello et al., 2017). D-aspartate was reported to promote the release of gonadotropin-releasing hormone by stimulating luteinizing hormone secretion in the pituitary gland (D'Aniello et al., 2000). Likewise, D-aspartate is positively associated with serum luteinizing hormone, androstenedione, and testosterone concentrations through increasing steroidogenic acute regulatory protein, P450 cholesterol side-chain cleavage enzyme, and 3b-hydroxysteroid dehydrogenase/D5-D4 isomerases gene expressions in rat testis and Leydig cells (Raucci et al., 2014).

4. D-aspartate in diseases

Due to antioxidant potential, D-aspartate plays an important role in the endocrine and nervous system to prevent or treat neurological diseases and reproductive diseases (Afraei et al., 2017; Boccella et al., 2015;D'Aniello et al., 2017). D-aspartate regulates nociceptive specific neuron electrophysiological activity and behavior to reflect the pain conditions (Boccella et al., 2015). Meanwhile, D-aspartate also serves as a pharmacological tool in

chronic pain to relieve related psychiatric condition, including Alzheimer's disease (D'Aniello et al., 2017). Injection of D-aspartate has a sedative effect with and without a hypnotic effect (Erwan et al., 2014). The potential mechanism may be that D-aspartate can activate NMDAR-mediated neurotransmission in the core of the postsynaptic density and then enhances glutamate signaling in the postsynaptic site, which is responsible to antipsychotic and schizophrenia treatment (de Bartolomeis et al., 2015).

5. Conclusion

D-aspartate is widely detected in animals and human with D-enantiomers and can be metabolized by D-aspartate racemase and DDO. D-aspartate mainly serves as a neurotransmitter and plays important roles in growth performance, reproduction, nervous, and endocrine mediatory functions, whereas the effects of D-aspartate on intestinal absorption and mechanism of feed intake need further studies.

Conflicts of interest

No potential conflicts of interest were reported by the authors.

Acknowledgments

This study was supported by Hunan Province key research and development projects (2017NK2321), National Basic Research Program of China (973) (2013CB127301), National Natural Science Foundation of China (31472106), and China Agriculture Research System (CARS-35).

References

Adachi M, Koyama H, Long Z, Sekine M, Furuchi T, Imai K, et al. L-Glutamate in the extracellular space regulates endogenous D-aspartate homeostasis in rat pheochromocytoma MPT1 cells. Arch Biochem Biophys 2004;424(1):89–96. https://doi.org/10.1016/j.abb.2004.01.016.

Afraei S, D'Aniello A, Sedaghat R, Ekhtiari P, Azizi G, Tabrizian N, et al. Therapeutic effects of D-aspartate in a mouse model of multiple sclerosis. J Food Drug Anal 2017;25(3):699–708. https://doi.org/10.1016/j.jfda.2016.10.025.

Ansari M, Zhandi M, Kohram H, Zaghari M, Sadeghi M, Sharafi M. Improvement of post-thawed sperm quality and fertility of Arian rooster by oral administration of d-aspartic acid. Theriogenology 2017;92:69–74. https://doi.org/10.1016/j.theriogenology.2017.01.014.

Barbato V, Talevi R, Braun S, Merolla A, Sudhakaran S, Longobardi S, et al. Supplementation of sperm media with zinc, D-aspartate and co-enzyme Q10 protects bull sperm against exogenous oxidative stress and improves their ability to support embryo development. Zygote 2017;25(2):168–75. https://doi.org/10.1017/S0967199416000459.

Berg CP. Physiology of the D-amino acids. Ark Patol 1953;33(2):145–89.

Boccella S, Vacca V, Errico F, Marinelli S, Squillace M, Guida F, et al. D-aspartate modulates nociceptive-specific neuron activity and pain threshold in inflammatory and neuropathic pain condition in mice. BioMed Res Int 2015;2015:905906. https://doi.org/10.1155/2015/905906.

Chung SY, Reed S. IgE binding to peanut allergens is inhibited by combined D-aspartic and D-glutamic acids. Food Chem 2015;166:248–53. https://doi.org/10.1016/j.foodchem.2014.06.004.

Cristino L, Luongo L, Squillace M, Paolone G, Mango D, Piccinin S, et al. d-Aspartate oxidase influences glutamatergic system homeostasis in mammalian brain. Neurobiol Aging 2015;36(5):1890–902. https://doi.org/10.1016/j.neurobiolaging.2015.02.003.

D'Aniello A. D-Aspartic acid: an endogenous amino acid with an important neuroendocrine role. Brain Res Rev 2007;53(2):215–34. https://doi.org/10.1016/j.brainresrev.2006.08.005.

D'Aniello A, Di Fiore MM, Fisher GH, Milone A, Seleni A, D'Aniello S, et al. Occurrence of D-aspartic acid and N-methyl-D-aspartic acid in rat neuroendocrine tissues and their role in the modulation of luteinizing hormone and growth hormone release. Faseb J Official Publ Fed Am Soc Exp Biol 2000;14(5):699–714.

D'Aniello A, Giuditta A. Identification of D-aspartic acid in the brain of Octopus vulgaris Lam. J Neurochem 1977;29(6):1053–7.

D'Aniello A, Luongo L, Romano R, Iannotta M, Marabese I, Boccella S, et al. D-Aspartic acid ameliorates painful and neuropsychiatric changes and reduces beta-amyloid Abeta1-42 peptide in a long lasting model of neuropathic pain. Neurosci Lett 2017. https://doi.org/10.1016/j.neulet.2017.04.041.

D'Aniello A, Vetere A, Petrucelli L. Further study on the specificity of D-amino acid oxidase and D-aspartate oxidase and time course for complete oxidation of D-amino acids. Comp Biochem Physiol B 1993;105(3-4):731–4.

D'Aniello G, Grieco N, Di Filippo MA, Cappiello F, Topo E, D'Aniello E, et al. Reproductive implication of D-aspartic acid in human pre-ovulatory follicular fluid. Hum Reprod 2007;22(12):3178–83. https://doi.org/10.1093/humrep/dem328.

D'Aniello G, Ronsini S, Guida F, Spinelli P, D'Aniello A. Occurrence of D-aspartic acid in human seminal plasma and spermatozoa: possible role in reproduction. Fertil steril 2005;84(5):1444–9. https://doi.org/10.1016/j.fertnstert.2005.05.019.

D'Aniello S, Somorjai I, Garcia-Fernandez J, Topo E, D'Aniello A. D-Aspartic acid is a novel endogenous neurotransmitter. FASEB journal. Official Publ Fed Am Soc Exp Biol 2011;25(3):1014–27. https://doi.org/10.1096/fj.10-168492.

D'Aniello S, Garcia-Fernàndez J. D-Aspartic acid and L-amino acids in the neural system of the amphioxus Branchiostoma lanceolatum. Amino Acids 2006;32(1):21–6. https://doi.org/10.1007/s00726-006-0347-5.

de Bartolomeis A, Errico F, Aceto G, Tomasetti C, Usiello A, Iasevoli F. D-aspartate dysregulation in Ddo(-/-) mice modulates phencyclidine-induced gene expression changes of postsynaptic density molecules in cortex and striatum. Prog Neuro-Psychopharmacol Biol Psychiatry 2015;62:35–43. https://doi.org/10.1016/j.pnpbp.2015.05.003.

Di Fiore MM, Santillo A, Chieffi Baccari G. Current knowledge of D-aspartate in glandular tissues. Amino Acids 2014;46(8):1805–18. https://doi.org/10.1007/s00726-014-1759-2.

Di Fiore MM, Santillo A, Falvo S, Longobardi S, Chieffi Baccari G. Molecular Mechanisms Elicited by d-Aspartate in Leydig Cells and Spermatogonia. Int J Mol Sci 2016;17(7). https://doi.org/10.3390/ijms17071127.

Errico F, Mothet JP, Usiello A. D-Aspartate: An endogenous NMDA receptor agonist enriched in the developing brain with potential involvement in schizophrenia. J Pharmaceut Biomed Anal 2015;116:7–17. https://doi.org/10.1016/j.jpba.2015.03.024.

Errico F, Napolitano F, Squillace M, Vitucci D, Blasi G, de Bartolomeis A, et al. Decreased levels of D-aspartate and NMDA in the prefrontal cortex and striatum of patients with schizophrenia. J Psychiatr Res 2013;47(10):1432–7. https://doi.org/10.1016/j.jpsychires.2013.06.013.

Errico F, Nistico R, Di Giorgio A, Squillace M, Vitucci D, Galbusera A, et al. Free D-aspartate regulates neuronal dendritic morphology, synaptic plasticity, gray matter volume and brain activity in mammals. Transl Psychiatry 2014;4. https://doi.org/10.1038/tp.2014.59. e417.

Errico F, Nistico R, Napolitano F, Mazzola C, Astone D, Pisapia T, et al. Increased D-aspartate brain content rescues hippocampal age-related synaptic plasticity deterioration of mice. Neurobiol Aging 2011a;32(12):2229–43. https://doi.org/10.1016/j.neurobiolaging.2010.01.002.

Errico F, Nistico R, Napolitano F, Oliva AB, Romano R, Barbieri F, et al. Persistent increase of D-aspartate in D-aspartate oxidase mutant mice induces a precocious hippocampal age-dependent synaptic plasticity and spatial memory decay. Neurobiol Aging 2011b;32(11):2061–74. https://doi.org/10.1016/j.neurobiolaging.2009.12.007.

Erwan E, Chowdhury VS, Nagasawa M, Goda R, Otsuka T, Yasuo S, et al. Central injection of L- and D-aspartate attenuates isolation-induced stress behavior in chicks possibly through different mechanisms. Eur J Pharmacol 2014;736:138–42. https://doi.org/10.1016/j.ejphar.2014.04.042.

Erwan E, Tomonaga S, Ohmori T, Mutaguchi Y. Oral Administration of D-aspartate, but not of L-aspartate, reduces food intake in Chicks. J Poultry Sci 2013;50(2):164–71. https://doi.org/10.2141/.

Fiore MMD, Santillo A, Falvo S, Baccari GC, Venditti M, Venditti M, Russo FDG, et al. Sex hormone levels in the brain of d -aspartate-treated rats. Comptes Rendus Biologies 2017;341(1).

Fisher G, Lopez S, Peterson K, Goff T, Philip I, Gaviria R, et al. Is there a correlation between age and D-aspartic acid in human knee cartilage? Amino Acids 2006;32(1):27–30. https://doi.org/10.1007/s00726-006-0353-7.

Fujii N, Kaji Y, Fujii N. D-Amino acids in aged proteins: analysis and biological relevance. J Chromatogr B Anal Tech Biomed Life Sci 2011;879(29):3141–7. https://doi.org/10.1016/j.jchromb.2011.05.051.

Giacone F, Condorelli RA, Mongioi LM, Bullara V, La Vignera S, Calogero AE. In vitro effects of zinc, D-aspartic acid, and coenzyme-Q10 on sperm function. Endocrine 2017;56(2):408–15. https://doi.org/10.1007/s12020-016-1013-7.

Han H, Miyoshi Y, Koga R, Mita M, Konno R, Hamase K. Changes in D-aspartic acid and D-glutamic acid levels in the tissues and physiological fluids of mice with various D-aspartate oxidase activities. J Pharmaceut Biomed Anal 2015;116:47–52. https://doi.org/10.1016/j.jpba.2015.05.013.

Katane M, Homma H. D-Aspartate—an important bioactive substance in mammals: a review from an analytical and biological point of view. J Chromatogr B Anal Tech Biomed Life Sci 2011;879(29):3108–21. https://doi.org/10.1016/j.jchromb.2011.03.062.

Kim PM, Duan X, Huang AS, Liu CY, Ming GL, Song H, et al. Aspartate racemase, generating neuronal D-aspartate, regulates adult neurogenesis. Proc Natl Acad Sci USA 2010;107(7):3175–9. https://doi.org/10.1073/pnas.0914706107.

Koyama H, Sekine M, Furuchi T, Katane M, Nimura N, Shimamoto K, et al. A novel L-glutamate transporter inhibitor reveals endogenous D-aspartate homeostasis in rat pheochromocytoma MPT1 cells. Life Sci 2005;76(25):2933–44. https://doi.org/10.1016/j.lfs.2004.10.057.

Krashia P, Ledonne A, Nobili A, Cordella A, Errico F, Usiello A, et al. Persistent elevation of D-Aspartate enhances NMDA receptor-mediated responses in mouse substantia nigra pars compacta dopamine neurons. Neuropharmacology 2016;103:69–78. https://doi.org/10.1016/j.neuropharm.2015.12.013.

Lamanna C, Assisi L, Botte V, Di Fiore MM. Involvement of D-Asp in P450 aromatase activity and estrogen receptors in boar testis. Amino Acids 2006;32(1):45–51. https://doi.org/10.1007/s00726-006-0351-9.

Lamanna C, Assisi L, Vittoria A, Botte V, Di Fiore MM. D-Aspartic acid and nitric oxide as regulators of androgen production in boar testis. Theriogenology 2007;67(2):249–54. https://doi.org/10.1016/j.theriogenology.2006.07.016.

Masuda W, Nouso C, Kitamura C, Terashita M, Noguchi T. Free d-aspartic acid in rat salivary glands. Archives Biochem Biophys 2003;420(1):46–54. https://doi.org/10.1016/j.abb.2003.09.032.

Matsuda S, Katane M, Maeda K, Kaneko Y, Saitoh Y, Miyamoto T, et al. Biosynthesis of D-aspartate in mammals: the rat and human homologs of mouse aspartate racemase are not responsible for the biosynthesis of D-aspartate. Amino Acids 2015;47(5):975–85. https://doi.org/10.1007/s00726-015-1926-0.

Molinaro G, Pietracupa S, Di Menna L, Pescatori L, Usiello A, Battaglia G, et al. D-aspartate activates mGlu receptors coupled to polyphosphoinositide hydrolysis in neonate rat brain slices. Neurosci Lett 2010;478(3):128–30. https://doi.org/10.1016/j.neulet.2010.04.077.

Motoie R, Fujii N, Tsunoda S, Nagata K, Shimo-oka T, Kinouchi T, et al. Localization of D-beta-aspartyl residue-containing proteins in various tissues. Int J Mol Sciences 2009;10(5):1999–2009. https://doi.org/10.3390/ijms10051999.

Muzzolini A, Bregola G, Bianchi C, Beani L, Simonato M. Characterization of glutamate and [3H]D-Aspartate outflow from various in vitro, preparations of the rat hippocampus. Neurochem Int 1997;31(1):113–24.

Opere CA, Monjok EM, Kulkarni KH, Njie YF, Ohia SE. Regulation of [3H] D-aspartate release from mammalian isolated retinae by hydrogen sulfide. Neurochemical Research 2009;34(11):1962–8. https://doi.org/10.1007/s11064-009-9984-x.

Ota N, Shi T, Sweedler JV. D-Aspartate acts as a signaling molecule in nervous and neuroendocrine systems. Amino Acids 2012;43(5):1873–86. https://doi.org/10.1007/s00726-012-1364-1.

Palazzo E, Luongo L, Guida F, Marabese I, Romano R, Iannotta M, et al. D-Aspartate drinking solution alleviates pain and cognitive impairment in neuropathic mice. Amino Acids 2016;48(7):1553–67. https://doi.org/10.1007/s00726-016-2205-4.

Punzo D, Errico F, Cristino L, Sacchi S, Keller S, Belardo C, et al. Age-related changes in D-aspartate oxidase promoter methylation control extracellular D-aspartate levels and prevent precocious cell death during brain aging. J Neurosci 2016;36(10):3064–78. https://doi.org/10.1523/JNEUROSCI.3881-15.2016.

Raucci F, D'Aniello A, Di Fiore MM. Stimulation of androgen production by D-aspartate through the enhancement of StAR, P450scc and 3beta-HSD mRNA levels in vivo rat testis and in culture of immature rat Leydig cells. Steroids 2014;84:103–10. https://doi.org/10.1016/j.steroids.2014.03.016.

Santillo A, Falvo S, Chieffi P, Burrone L, Chieffi Baccari G, Longobardi S, et al. D-aspartate affects NMDA receptor-extracellular signal-regulated kinase pathway and upregulates androgen receptor expression in the rat testis. Theriogenology 2014;81(5):744–51. https://doi.org/10.1016/j.theriogenology.2013.12.009.

Santillo A, Falvo S, Chieffi P, Di Fiore MM, Senese R, Chieffi Baccari G. D-Aspartate Induces Proliferative Pathways in Spermatogonial GC-1 Cells. J Cell Physiol 2016;231(2):490–5. https://doi.org/10.1002/jcp.25095.

Savage DDGR, Queen SA, Paxton LL, Allan AM. Characterization of electrically evoked [3H]-D-aspartate release from hippocampal slices. Neurochem Int 2001;38(3):255–67.

Tanaka-Hayashi A, Hayashi S, Inoue R, Ito T, Konno K, Yoshida T, et al. Is D-aspartate produced by glutamic-oxaloacetic transaminase-1 like 1 (Got1l1): a putative aspartate racemase? Amino Acids 2015;47(1):79–86. https://doi.org/10.1007/s00726-014-1847-3.

Van Veldhoven PPBC, Mannaerts GP. D-aspartate oxidase, a peroxisomal enzyme in liver of rat and man. Biochim Biophys Acta 1991;1073(1):203–8.

Zhang Z, Yuan L, Liu Q, Cai B, Li X, Zhao H, et al. Biosafety assessment of genetically modified foods based on the toxicology of the chiral D-amino acid. Scientia Sinica Chimica 2015;45(1):98.