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BRAIN RESEARCH REVIEWS

Review

D-Aspartic acid: An endogenous amino acid with an important neuroendocrine role

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ABSTRACT

D-Aspartic acid (D-Asp), an endogenous amino acid present in vertebrates and invertebrates, plays an important role in the neuroendocrine system, as well as in the development of the nervous system. During the embryonic stage of birds and the early postnatal life of mammals, a transient high concentration of D-Asp takes place in the brain and in the retina. D-Asp also acts as a neurotransmitter/neuromodulator. Indeed, this amino acid has been detected in synaptosomes and in synaptic vesicles, where it is released after chemical (K^+ ion, ionomycin) or electric stimuli. Furthermore, D-Asp increases cAMP in neuronal cells and is transported from the synaptic clefts to presynaptic nerve cells through a specific transporter. In the endocrine system, instead, D-Asp is involved in the regulation of hormone synthesis and release. For example, in the rat hypothalamus, it enhances gonadotropin-releasing hormone (GnRH) release and induces oxytocin and vasopressin mRNA synthesis. In the pituitary gland, it stimulates the secretion of the following hormones: prolactin (PRL), luteinizing hormone (LH), and growth hormone (GH) In the testes, it is present in Leydig cells and is involved in testosterone and progesterone release. Thus, a hypothalamus–pituitary–gonads pathway, in which D-Asp is involved, has been formulated. In conclusion, the present work is a summary of previous and current research done on the role of D-Asp in the nervous and endocrine systems of invertebrates and vertebrates, including mammals.

Contents

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1. Introduction: stereochemical consideration on D-amino acids

Stereochemical configuration of the α-carbon atom of amino acids is fundamental to all living systems. All the amino acids found in proteins (except for glycine) are optically active and have the same stereochemical configuration as the α-carbon atom. The prefix L attached to these amino acids goes back to half a century ago when Louis Pasteur in 1851 (Pasteur, 1851) observed that asparagine, the first natural amino acid discovered by Vauquelin and Robiquet in 1806 (Vauquelin and Robiquet, 1806), was "levorotatory", i.e., able to disperse the polarized light to the left. On the other hand, the prefix D indicated that the amino acids were able to rotate the polarized light to the right. Although Pasteur forcefully pointed out that the natural asparagine was different from the synthetic one, he failed to recognize that the synthetic molecule was a racemic mixture, which recalled the racemic form of tartaric acid that he himself had previously studied. However, Greenstein (1954) and Greenstein et al. (1953) later observed that not all natural amino acids had the same effect on the dispersion of light. Therefore, in an attempt to clarify the nomenclature of the amino acids, the capitals L- and D- were used to refer to the configurations of the α-carbon atom: the L-amino acid (L-form) designation was given to the natural amino acids, whereas the D-amino acid (D-form) designation was given to those amino acids having opposite spatial configurations of the α-carbon atom (obtained by X-ray diffraction) (Greenstein et al., 1953). Furthermore, since L-amino acids have the same spatial form as L-glyceraldehyde, all compounds with an asymmetric carbon atom similar to L-glyceraldehyde were designed as L-forms, whereas those opposite in configuration were designed as D-forms (Fig. 1). In addition to the chemical considerations, it has also been observed that only the L-amino acids are biologically oxidized by L-amino acid oxidase (L-AAO; EC 1.4.3.2) (Bender et al., 1949; Blaschko and Newkim, 1952). By contrast, the D-amino acids are oxidized by other oxidases. Specifically, D-aspartic acid (D-Asp), D-glutamic acid (D-Glu), and *N*-methyl-D-aspartic acid (NMDA) are oxidized by a D-aspartate oxidase (D-AspO; EC 1.4.3.1) (D'Aniello et al., 1993c; Dixon et al., 1967), whereas all the other D-amino acids are oxidized by a D-amino acid oxidase (D-AAO; EC 1.4.3.3) (D'Aniello et al., 1993c; Dixon and Kleppe, 1965). Then, since no free D-amino acids were found in plants or animals, it was believed that only the L-amino acids were natural compounds. However, during the last half of the 20th century, by using specific enzymatic methods based on the use of D-AspO, D-AAO and HPLC techniques, many D-amino acids, in particular D-Asp, D-Ser and D-Ala, were discovered in free compounds or bound to peptides and proteins in bacteria, moulds, vertebrates, and invertebrates (Corrigan, 1969; Meister et al., 1965). The present study has gleaned some of the most recent breakthroughs in the study of D-Asp in an attempt to highlight its prominent role in the development of the nervous and endocrine systems during the embryonic stages or the early postnatal stages of animals.

2. D-Amino acids in peptides and proteins

The first D-amino acids detected in living organisms were discovered in some plants and bacteria about 50 years ago (Corrigan, 1969; Meister et al., 1965). These compounds were either found in a free state or were incorporated in peptides and protein linkages. Indeed, a number of antibiotics (e.g., polymixin, bacitracin, gramicidin, actinomycins, etc.) and bacterial cell walls contain D-amino acid residues in peptides bound to L-amino acids. In the last case, D-amino acids seem to constitute a measure of protection against peptidase and protease attacks, since, so far, no known protease has been shown to cleave peptide bonds, characterized by a sequence of amino acids in D-D or D-L conformation (Corrigan, 1969; Meister et al., 1965). Only one peptidase, capable of hydrolyzing bonds involving D-amino acids, has been purified from the intestinal sac of some marine mollusks (D'Aniello and Strazzullo, 1984). D-Phe and D-Asn occur in the two peptides: Gly-D-Phe-L-Ala-L-Asp and L-Phe-D-Asn-L-Glu-L-Phe-L-Val. Because they are both found in the cerebral ganglia of the mollusk *Achatina fulica* (Corrigan, 1969; Meister et al., 1965), they contribute to the

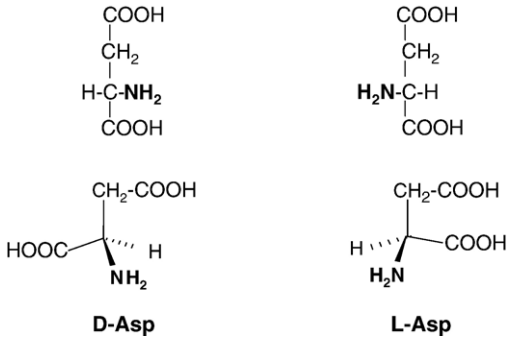

Fig. 1 – Stechiometric representation of D-Asp and L-Asp using a linear formulae (upper panel) and carbonium presentation based on the tetrahedral configuration (lower panel).