trapolated to humans and placed in an SQL community database by David Van Essen and colleagues. This will make it suitable for federation with BrainMap, SPMap, and other emerging community databases. Further promoting interproject coordination, developers of several neuroscience and genetics databases sit on the BrainMap Advisory Group. Similarly, the developers of BrainMap (P.T.F. and J.L.L.) collaborate on several emerging HBP-funded neuroscience databases.

Thus, despite its youth, the neuroscience informatics community can boast a vision of federation, agreement on a syntax that will support federation, and well-advanced interproject coordination. This is already in strong contrast to the genome community, where no two of the major community databases (Genome Data Base, GenBank, PIR-International, PDB) "are funded by the same program, advised by the same advisors, or otherwise coordinated" (*3*). Nevertheless, the greatest hurdle, that of semantic coordination, remains before us. This is being addressed through a series of annual workshops (*11*). The next workshop, *Database Development in Brain and Behavior*, will take place in San Antonio, 4 and 5 December 1994. Federation and plans to achieve it will be the order of the day.

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13. We thank R. Lucier for many conversations on database theory and practice; R. Robbins, P. Gilna, and C. Fields for conversations on database federation; L. Parsons, S. Harnad, and S. Mikiten for insights into the Internet culture; and J. Sergent for unwavering support of BrainMap and the community database concept. This work was supported by a grant from the EJLB Foundation.

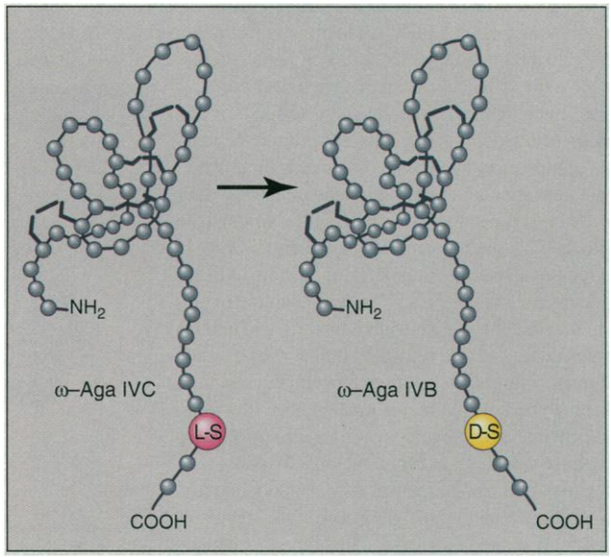
Conversion of L- to D-Amino Acids: A Posttranslational Reaction

Günther Kreil

Living organisms synthesize proteins composed of L-amino acids. But on page 1065 of this issue, Heck and colleagues describe an enzymatic activity that converts an L-amino acid to its D form in a peptide from spider venom. Is this a bizarre exception? Probably not. It now seems prudent to consider that D-amino acids can be present in the sequences of secreted peptides of diverse origin.

D-amino acids do occur in bacterial peptides. More than 50 years ago, Lipmann—who was then collaborating with Hotchkiss and Dubos, two pioneers of the early antibiotic era—demonstrated that the small peptides tyrocidine and gramicidine contained D-amino acids (*1*). Many years later, Lipmann and his co-workers investigated the biosynthesis of these antibiotic peptides and showed that they are assembled in a stepwise fashion by multienzyme complexes without the participation of messenger RNAs and ribosomes (*2*, *3*). The peptide bonds are formed via intermediate aminoacylthioesters.

A second group of D-amino acid–containing peptide antibiotics—the lantibiotics—were first analyzed in the laboratory of E. Gross in the 1970s (*4*). These contain many unusual amino acids, including lanthionine. At least some of these peptides are derived from larger precursors assembled on ribosomes. A multitude of modifications of the primary translation product then yields the final products. Some of the serine and threonine residues are converted to the corresponding dehydro amino acid and, upon subsequent addition of thiol groups from cysteine residues in the same sequence, the chirality of the α-carbon changes from the L- to the D-configuration (*5*).



Schematic representation of two spider venom toxins. Peptide IVB is generated from IVC by conversion of an L-serine to the D-isomer.

The report by Heck *et al.* (*6*) in this issue is the latest addition to a different story, which began in 1981. At that time a group of Italian scientists described the sequence of an opioid peptide isolated from skin of a South American tree frog, *Phyllomedusa sauvagei* (*7*). This heptapeptide—dermorphin—has the amino-terminal sequence Tyr-D-Ala-Phe. It has a high affinity and selectivity for the μ-type of opiate receptors, and upon injection into the brains of rats and mice acts about a thousand times more effectively than morphine producing long lasting, deep analgesia (*7*). The D-amino acid is essential for the biological activity of dermorphin. Several additional peptides containing a D-alanine, D-methionine, or D-leucine as the second amino acid have since been isolated from the skin of *Phyllomedusa* species (*8*, *9*). Some of these resemble dermorphin in their biological activity, while another group of peptides, the deltorphins, are highly selective agonists for δ receptors. More recently, a family of antimicrobial peptides termed bombinins H (*10*) was isolated from the skin of another frog species, *Bombina variegata*. Some of the members of this family contain D-alloisoleucine instead of isoleucine. Several peptides containing a D-amino acid have also been

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isolated from invertebrates. These include fulicin and achatin from snail ganglia, which contain D-asparagine and D-phenylalanine, respectively (*11*, *12*). These peptides from amphibia and mollusks have diverse functions and sequences; the only common feature is that in all instances the D-amino acid is present at the second position of the end product.

Nevertheless, this is not a general rule for peptides of this type. The hyperglycemic hormone from two species of crustaceans occurs in two variants, with either L- or D-phenylalanine as the third residue (*13*, *14*). Another example is the peptide described on page 1065 of this issue. The venom of the funnel web spider *Agelenopsis aperta* contains peptides that paralyze prey by blocking N- and P-type voltage-sensitive calcium channels. Two of these toxins, ω-agatoxins IVC and IVB, differ from each other by the presence of either L- or D-serine at position 46.

How are these peptides synthesized in eukaryotic cells? A few years after its discovery, it was shown that dermorphin was derived from larger precursor polypeptides. In the cloned complementary DNAs encoding these precursors, a normal codon for L-alanine is present in those positions where a D-alanine occurs in the final product (*15*). This is also true for the other peptides of this group. For example, the D-alloisoleucine present in several bombinins H is derived from isoleucine in the precursor (*10*). Thus, at some stage in the processing of the precursors of these peptides, certain L-amino acids are converted to the D-isomer. What could be the mechanism of this most unusual posttranslational reaction?

Heck *et al.* (*6*) provide a first clue. The venom of the funnel web spider contains an enzymatic activity that slowly interconverts the two forms of the toxin. Upon incubation of ω-agatoxin IVC with a venom fraction containing mainly a polypeptide with a molecular mass of 29 kD, the L-serine at position 46 is slowly converted to the D-isomer. The enzymatic reaction proceeds in both directions, albeit with somewhat different rates, and it is independent of externally added cofactors. Nothing is known about its mechanism. The authors speculate that this conversion of an L- to the D-amino acid in the peptide linkage may proceed via a two-base mechanism, whereby the proton of the α-carbon of an amino acid is removed from one side and added to the other side. Several amino acid racemases function in this way [see for example (*16*)]. However, the enzyme is not a racemase in the strict sense, because the two products are diastereomers, not enantiomers. By analogy to peptidyl prolyl cis-trans isomerase, the enzyme could thus be called a peptidyl aminoacyl L-D-isomerase. What remains completely puzzling is the specificity of this enzyme. It recognizes a particular serine residue close to the carboxyl-terminal end of these agatoxins, but it does not change the chirality of any of the adjacent amino acids. Other enzymes of this class with different substrate specificities may synthesize the D-amino acid–containing peptides from other sources.

The presence of D-amino acids may serve several purposes. First, new three-dimensional structures can be formed that cannot be built from L-amino acids only. The sequence Tyr-D-XXX-Phe in dermorphins and deltorphins has a type II′ β-turn structure, where part of the side chain of the D-amino acid is sandwiched between the two aromatic residues (*17*). This may be one reason why the Tyr-D-Ala-Phe-sequence can bind to the same receptors as the enkephalins with the amino-terminal sequence Tyr-Gly-Gly-Phe. A similar structure has been found by x-ray crystal analysis for the Gly-D-Phe-Ala sequence in achatin-I (*18*). It is not surprising that such an essential structural component is absolutely necessary for biological activity, that is, for binding to receptor polypeptides. Second, the D-residue may modulate the biological activity of a peptide in a subtle way, thereby increasing the biological diversity encoded by a single gene. For example, the time course of action of the two variants of the hyperglycemic hormone from lobster is different for the L- and the D-phenylalanine forms (*13*). The activities of the two agatoxins differ depending on the chirality of the serine residue. The D-form is three to five times more active than the L-isomer. Last, the presence of D-amino acids may simply increase the biological half-life of peptides, as bonds adjacent to such residues are not hydrolyzed by most exo- or endoproteases. The L-amino acid–containing dermorphins and deltorphins are present, if at all, only in trace amounts, as they are likely degraded rapidly. The bombinins H and agatoxin containing the D-isoforms also seem to be more stable.

The new isomerase may well represent the beginning of an interesting chapter in enzyme biochemistry. After all, changing the chirality of an amino acid in a peptide linkage is a feat not even organic chemists can accomplish at present.

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