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Review

Ureases as multifunctional toxic proteins: A review

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ABSTRACT

Ureases are metalloenzymes that hydrolyze urea into ammonia and carbon dioxide. They were the first enzymes to be crystallized and, with them, the notion that enzymes are proteins became accepted. Novel toxic properties of ureases that are independent of their enzyme activity have been discovered in the last three decades. Since our first description of the neurotoxic properties of canatoxin, an isoform of the jack bean urease, which appeared in *Toxicon* in 1981, about one hundred articles have been published on "new" properties of plant and microbial ureases. Here we review the present knowledge on the non-enzymatic properties of ureases. Plant ureases and microbial ureases are fungitoxic to filamentous fungi and yeasts by a mechanism involving fungal membrane permeabilization. Plant and at least some bacterial ureases have potent insecticidal effects. This entomotoxicity relies partly on an internal peptide released upon proteolysis of ingested urease by insect digestive enzymes. The intact protein and its derived peptide(s) are neurotoxic to insects and affect a number of other physiological functions, such as diuresis, muscle contraction and immunity. In mammal models some ureases are acutely neurotoxic upon injection, at least partially by enzyme-independent effects. For a long time bacterial ureases have been recognized as important virulence factors of diseases by urease-producing microorganisms. Ureases activate exocytosis in different mammalian cells recruiting eicosanoids and Ca^{2+}-dependent pathways, even when their ureolytic activity is blocked by an irreversible inhibitor. Ureases are chemotactic factors recognized by neutrophils (and some bacteria), activating them and also platelets into a pro-inflammatory "status". Secretion-induction by ureases may play a role in fungal and bacterial diseases in humans and other animals. The now recognized "moonlighting" properties of these proteins have renewed interest in ureases for their biotechnological potential to improve plant defense against pests and as potential targets to ameliorate diseases due to pathogenic urease-producing microorganisms.

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Abbreviations: 3D, tridimensional; CNS, central nervous system; ED_{50}, 50% effective dose; ip, intraperitoneal; LD_{50}, 50% lethal dose; CNTX, canatoxin; HPU, *Helicobacter pylori* urease; JBU, jack bean major urease; SBU, soybean urease; BPU, *Bacillus pasteurii* urease; GHU, cotton (*Gossypium hirsutum*) urease; PDB, Protein Data Bank; *p*HMB, *p*-hydroxy-mercurybenzoate.

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1. Urease, a milestone in the history of modern biochemistry

Ureases (urea amidohydrolases, EC 3.5.1.5) are nickel-dependent metalloenzymes that catalyze urea hydrolysis into ammonia and carbon dioxide, enhancing the rate of the uncatalyzed hydrolysis by a factor of 8×10^{17} (Callahan et al., 2005). Studies focusing on these enzymes have provided important milestones for modern biochemistry. The urease substrate, urea, was the first organic molecule synthesized in the laboratory (Wöhler, 1828). The study of the *Canavalia ensiformis* (jack bean) urease (JBU) crystals revealed the proteinaceous nature of enzymes (Sumner, 1926), laureating James B. Sumner with the 1946 edition of the Nobel Prize in Chemistry. Studies carried out with the same JBU protein also demonstrated for the first time that the transition metal nickel exerts a biological role in living organisms (Dixon et al., 1975; Zambelli et al., 2011). Besides JBU, *C. ensiformis* displays two additional isoforms of urease: canatoxin (Carlini and Guimaraes, 1981) and JBURE-II (Mulinari et al., 2011).

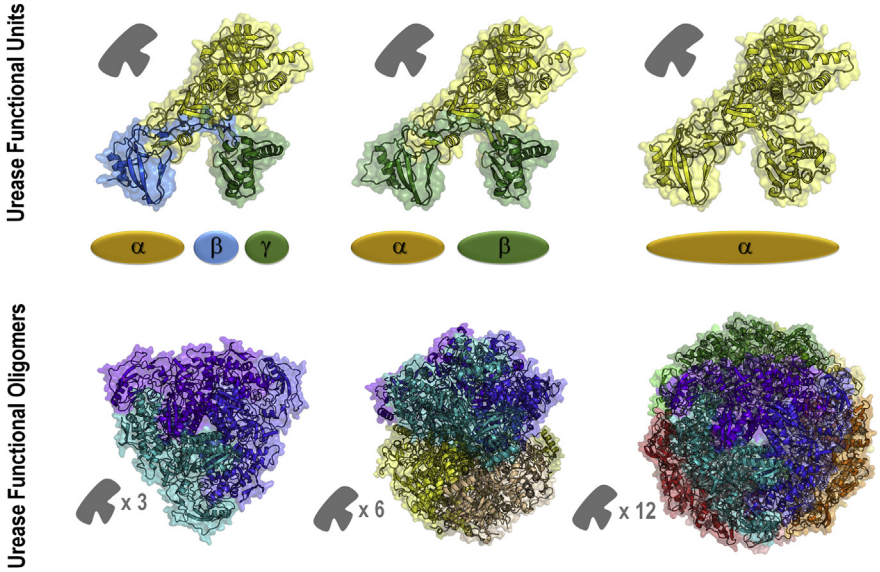

Fig. 1. The conserved structure of ureases. Ureases have a conserved functional unit structure, despite being formed by a variable number of subunits. A functional unit can be formed by a trimer of heterosubunits (as in *B. pasteurii*, PDB id 2UBP), by a dimer of heterosubunits (as in *H. pylori*, PDB id 1E9Z) or by a single unit (as in *C. ensiformis*, PDB id 3LA4). These functional units, in turn, can form larger complexes, such as trimers (PDB id 2UBP), hexamers (PDB id 3LA4), or dodecamers (PDB id 1E9Z).

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