J. Membrane Biol. 212, 69–70 (2006)
DOI: 10.1007/s00232-006-0866-8

The Journal of
Membrane
Biology

Thematic Issue

Urea Transport

Foreword

Otto Fröhlich
Department of Physiology, Emory University School of Medicine, Atlanta, GA 30322, USA

Accepted: 12 September 2006

When Friedrich Wöhler discovered in 1828 that he could convert the inorganic compound ammonium cyanate into the organic compound urea, he opened up the field of organic chemistry. Until then, urea was known only as a natural compound, isolated from urine, which apparently required the kidney for its formation. Of course, we now know that urea is produced in the liver, and that happens by an enzymatic mechanism quite distinct from how urea is produced industrially. However, the overall result is the same for both processes: urea, chemically also known as carbamide or carbonyl diamide, is the product of the condensation of ammonium and carbon dioxide (or carbonic acid), CO_2 being a physiologically readily available co-ingredient. As such, urea has become an important player in the handling of nitrogen in many organisms. For many vertebrates, urea synthesis and excretion has become the predominant means to get rid of the nitrogen resulting from food catabolism, although it is not the sole form of nitrogenous waste, with ammonium and uric acid also being available. Along the lines of ''one man's trash is another man's treasure'', it is also easy to see why urea that is excreted by animals could be a source of nitrogen for microorganisms and plants.

The theme of this issue of the Journal of Membrane Biology is the mechanisms by which urea is moved across biological membranes. With its carboxyl and amino groups, urea is polar and has early on been recognized as being fairly impermeant for bilayers – its permeability is about 1×10^{-6} cm s^{-1} at 25°C, somewhat less than expected from its oil/water partition coefficient (Finkelstein 1976). Therefore, whenever urea is supposed to enter or leave a cell, either rapidly or against its concentration gradient, it requires a transport protein that mediates this process. Nature had to invent means to move it across the bilayers, be it for cellular export or for import. The contributions to this volume elaborate on the different transport pathways that have evolved. Even more, they show how different organisms make use of urea in intricate ways that go beyond the scope of dealing with merely disposing of or acquiring a waste product or source of nitrogen, respectively.

The first contribution by Sachs and coworkers is a review of bacterial urea transport systems. Some bacteria possess multi-component ABC-type active transport systems through which urea is taken up under nitrogen-limited conditions. There exists also a single-peptide protein that permits passive urea entry in *Yersinia* and other species when the environment is rich in urea. Interestingly, this latter transporter, presumably a channel, has a weak sequence homology with the mammalian urea transporters. However, these two classes of urea transporters are not the really exciting ones. The main focus of this review is on the ureI urea channel found in *Helicobacter pylori*. This bacterium actually hijacks urea to a different purpose, namely to survive in the strongly acidic environment of the stomach. In conjunction with a highly active urease, this urea channel catalyzes urea entry followed by hydrolysis to ammonium, thus providing a buffer system that counteracts the acidic environment. And, of course, this activity is regulated by pH, thus permitting survival in less acidic environments as well.

The second review by Kojima and coworkers describes how urea is handled by plants as source of nitrogen. While ammonium and nitrate probably present the main contributors to soil nitrogen, most urea is broken down in the soil to ammonium, at least

Keywords: Urea transporters — Transporter family — Passive and active urea transport

Correspondence to: Otto Fröhlich; email: otto.froehlich@emory.edu

some plants also possess urea-transporting systems. One might expect that under urea-rich conditions there is a passive urea transport pathway. Indeed, as is also known from the animal kingdom, there are plant aquaporins that permit transport of urea. There is also an active urea uptake system different from the bacterial ABC-type system. The prototype for this transporter is the DUR3 protein of *Saccharomyces cerevisiae*. DUR3p is structurally related to the mammalian Na-dependent cotransporter family (SCL5A). By the way, urea entering the yeast cell is hydrolyzed by a dual-enzyme urease that is quite different from the bacterial urease mentioned above, another indication of the many ways nature has solved the problem of urea handling and processing.

Urea is not only a molecule whose purpose is to be excreted as metabolic nitrogen waste product or to be acquired as welcome source of nitrogen. As mentioned for *H. pylori*, urea can also be co-opted to participate in unrelated physiological processes. There are also several cases of co-option in vertebrates. In their review, McDonald and coworkers describe the different physiological roles of urea in fish. In principle, fish would not need to produce urea since they can excrete nitrogen in the form of ammonia, except in the relatively rare case of a strongly alkaline environment, but some species can still rapidly switch from ammonia to urea production. It is also fascinating to see how fish living in salt water use urea in their blood plasma as osmolyte to compensate for the high osmolarity environment, and use urea transport mechanisms in the kidney and gills to prevent excessive loss of urea.

In the human, urea is the major nitrogenous waste product under normal (non-acidotic) physiological conditions. And again, urea is co-opted for an important physiological process. As most land animals need to conserve body water, urea has been used in an intricate, not yet completely understood, mechanism to reduce water excretion by concentrating the urine. The urea transporter UTA, a member of the *Slc14A* gene family, is expressed in the kidney as several different alternative splicing variants in different tubule segments. Smith and Fenton review the genomic structure of the UT-A gene (*Slc14A2*) in the mouse, rat and human, and the different splicing variants derived from this gene. As there is strong sequence homology between the urea transporters found in fish and in mammals, one might expect overlap in the functional roles of the urea transporters in the kidneys of the two classes of animals, such as in the recycling of urea, but the mammalian UT's role goes further in that it contributes significantly to the renal concentration mechanism. Fenton and coworkers examine the function of the urea transporter forms UT-A1 and UT-A3 in this concentrating mechanism from the perspective obtained from knock-out animals. The possible functions of the other UT gene, UT-B or Slc14A1, which is more ubiquitously expressed in the body but found at very high concentration in red erythocytes, are reviewed by Bagnasco. Finally, to demonstrate the existence of the regulatory mechanism, some known and others yet to be elucidated, Klein and coworkers report on experimental findings of how the renal protein levels UT-A1 and the AQP2 water channel respond to steroid levels in normal and experimental diabetic animals.

These articles describe several mechanistically different transport pathways that mediate active or passive transport of urea. This highlights how nature has evolved means to get rid of nitrogenous waste and to recycle it in another organism. It also shows the ingenuity with which nature has made use of urea to accomplish physiological tasks without which the organism either could not exist at all or only under very favorable environmental conditions. It is quite possible that there are still additional urea transporters to be identified; there is evidence for one or possibly two active urea transporters in the mammalian kidney. And who knows how many more unexpected uses in some organisms this simple molecule may have that are yet waiting to be discovered.

Reference

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