Could you provide an insight into your research background?

I trained as a classical physiologist using techniques that endeavour to mimic the behaviour of a whole tissue or organ. The small intestine and kidneys are very complex organs that cannot be fully understood using molecular techniques alone, but combining both molecular and physiological approaches can be very powerful. We have used isolated tissues to try and understand how transport processes that result in absorption from the intestinal lumen to the blood are regulated by both hormones and nerves. To characterise the individual transport proteins, however, we express them in *Xenopus* oocytes (eggs) at very high levels to enable substrate flux and electrophysiology studies. By making amino acid mutations in the proteins, we can probe how the transporters interact with the hexoses and urate, with the goal of identifying potential sites for drug interactions.

What led you to develop an interest in urate homeostasis and hexose transport?

When the human genome sequence was published, the family of facilitated hexose transporters was identified as being far more diverse than previously suspected, and so we began to explore the characteristics of the class II members (GLUT5, GLUT7, GLUT9 and GLUT11), of which we had cloned GLUT7. We determined, in collaboration with a number of colleagues, that all these transporters handle fructose – a hexose in which we already had a research interest. This included GLUT9, which we had characterised with Dr Kelle Moley’s group at Washington University in St Louis, USA. Moley’s group has been studying members of the GLUT family for many years, and we have been working together ever since.

Subsequently, serendipity came into play: we were contacted by a major research group at the William Harvey Institute, UK, led by Dr Mark Caulfield. There, researchers employ genome scanning of large human populations to identify genes that could be linked to particular diseases – in this case, hypertension – and had identified a series of single point mutations in the gene for GLUT9. Caulfield asked if we would be interested in a collaboration to see how fructose, urate and GLUT9 were connected. The answer was a complete surprise: we found that this ‘hexose’ transporter was also a high capacity urate carrier.

Are you involved in any other research collaborations?

In addition to our work with Moley’s group at Washington University in St Louis and Caulfield’s group at the William Harvey Institute, I have another group of colleagues at the University of Alberta. We are working together to develop hexose-based probes to use for imaging breast and other cancers, and the team includes chemists, oncologists, radiopharmacists and physiologists.

To what extent is a multidisciplinary approach necessary to your work?

A multidisciplinary approach is essential. The combination of different techniques, methods and the opportunity to test ideas with others leads to far more creative solutions to problems and much more rapid progress.
The transporter

Cutting-edge research at the University of Alberta is investigating the underlying mechanisms of urate in a bid to develop new drugs to treat a range of conditions, including gout.

URATE IS A metabolic end product. In humans, it is vital that plasma urate levels remain balanced; high concentrations (hyperuricaemia) can lead to a number of illnesses such as gout – one of the oldest and most commonly recorded forms of arthritis in which urate crystals form in joints causing inflammation and severe pain. Furthermore, high blood urate has been linked to other medical conditions such as diabetes, cardiovascular diseases, hypertension and metabolic disease. Too little urate, meanwhile, can lead to hyperuricosuria (excessive urate in the urine) and cause kidney stones and metabolic disturbances.

To prevent either of these outcomes, plasma urate levels must be constantly regulated. The exact mechanisms through which this occurs, however, remain unclear. It is known that the liver is primarily responsible for urate production, while the kidneys play a role in its excretion, but what happens in between is not yet understood. It is these mechanisms that Dr Chris Cheeseman, along with his research group in the Department of Physiology at the University of Alberta, Canada, aims to elucidate.

GLUT9

Cheeseman is exploring the role that hexose transporters play in health and disease. His lab is conducting experiments into the hexoses glucose, galactose and fructose. Specifically, the team is currently focusing on the glucose transporter 9 (GLUT9), which is found mainly in the kidney, liver and colon and has been identified by his group as an important urate transporter.

In 2009, Cheeseman’s team proposed a novel model of urate reabsorption and excretion in which GLUT9 played a pivotal role. It was also at this time, as a result of fruitful collaborations with Dr Kelle Moley’s group at Washington University in St Louis, USA, and Dr Mark Caulfield’s team at the William Harvey Institute, UK, that the researchers identified three key features about GLUT9’s interactions with urate and hexoses. Firstly, they demonstrated that transport of urate across the cell membrane is driven by the membrane potential, suggesting that GLUT9 is more likely to release urate than take it up. Secondly, GLUT9 was found to be capable of exchanging hexoses with urates, thus accelerating the movement of both across the cell membrane. “This may play a role in metabolic disease, as elevated levels of plasma hexoses could promote efflux of urate from the liver into the blood,” Cheeseman speculates. Third, the team identified not one, but two forms of GLUT9; one expressed in the basolateral membrane in the proximal tubule and a second in the apical membrane of the distal tubule. “The implication is that the former is related to urate reabsorption, while the latter, positioned further along the tubule, is more likely related to regulating the final blood concentration by secreting some urate back into the urine if concentrations get too high,” he continues.

DEFINING MOLECULAR MECHANISMS

At present, the researchers are continuing to conduct research on GLUT9 and its role in urate homeostasis, determined to learn more about this fascinating protein. “GLUT9 appears to be unique amongst the GLUTs in that it can transport both hexoses and the organic anion urate,” Cheeseman highlights. Furthermore, as urate has been identified as a key metabolite, a better understanding of how it is handled by GLUT9 in the liver, kidneys and intestine may allow for deeper knowledge of its role and underlying mechanisms.
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URATE IMBALANCES

Abnormal urate levels within human blood plasma are associated with a number of medical conditions, including:

- Cardiovascular disease
- Hypertension
- Type 2 diabetes
- Metabolic syndrome
- Gout
- Kidney stones

MEDICAL APPLICATIONS

The current range of drugs used to treat conditions brought about by high levels of urate, generally target reabsorption of the urate across the kidney tubule by acting on the apical transporter URAT1. Consequently, Cheeseman and his team are investigating GLUT9’s potential to treat a number of related conditions: “There are few drugs available to reduce plasma urate or its accumulation in the joints, but if we can define the molecular mechanism by which GLUT9 handles urate, then we should be able to design new families of drugs to stop this occurring and so treat associated diseases more effectively,” he predicts.

To elucidate the molecular mechanisms of GLUT9, Cheeseman’s lab is addressing this fascinating task using a combined approach. The group is collaborating with Dr Joanna Lemieux of the University of Alberta’s Department of Biochemistry to generate 3D computer models of the molecule and simulate how the substrates might interact with it during transport. “This allows us to identify key residues within the structure that we can mutate individually or in combination,” Cheeseman expounds. “These mutated proteins are then expressed in the oocytes and tested for their activity and characteristics. In this way we can identify the key elements of GLUT9 and how it differs from its family members.”

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Even without such exciting potential translational benefits on the horizon, a better understanding of GLUT9 and of urate homeostasis generally will surely have a positive impact for science and society. Fundamental discoveries in this area are still to be made, and it is impossible to predict what may be learnt next about this one small protein.

A PRIMATE PUZZLE

While almost all mammals possess an enzyme called uricase that can convert urate into allantoin (a highly soluble excretory product), in humans and primates the uricase gene is inactive. This means that urate can be found in much higher quantities in the blood of humans and primates than in other mammals.

The basis for this difference, however, remains unknown. “It’s a real puzzle,” admits Dr Chris Cheeseman. “As Jared Diamond points out in his book *The Third Chimpanzee*, our genomes differ by so little that this difference suggests our metabolism has some kind of unique requirement. Urate is an effective antioxidant, and it has been proposed it might offer some kind of protection for our larger brains during our relatively extended lifespan. But to be truthful, we are still unable to provide a meaningful explanation.”

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