Researchers discover that SLC2A9 is a high-capacity urate transporter in humans

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An international team of researchers led by Professors Mark Caulfield and Patricia Munroe, from the William Harvey Research Institute at Barts and The London School of Medicine and Dentistry with Chris Cheeseman at the University of Alberta in Canada and Kelle Moley at the University of Washington in USA, have shown that the SLC2A9 gene, which encodes a glucose transporter, is also a high-capacity urate transporter, and thus possibly a new drug target for gout. Their findings are published in this week's *PLoS Medicine* (7 October 2008).

The team first expressed SLC2A9 in frog eggs, a type of cell that does not have its own urate transporter. They found that SLC2A9 transported urate about 50 times faster than glucose, and that glucose facilitated SLC2A9-mediated urate transport. Similarly, over expression of SLC2A9 in human embryonic kidney cells more than doubled their urate uptake. Conversely, when the researchers used a technique called RNA interference to reduce the expression of mouse SLC2A9 in mouse cells that normally makes this protein, urate transport was reduced. Researchers then looked at two genetic variations within SLC2A9 that vary between individuals (so-called single polynucleotide polymorphisms) in nearly 900 men who had had their serum urate levels and urinary urate excretion rates measured. They found that certain genetic variations at these two sites were associated with increased serum urate levels and decreased urinary urate excretion. Finally, the researchers used a statistical technique called meta-analysis to look for an association between one of the SLC2A9 gene variants and blood pressure. In two separate meta-analyses that together involved more than

20,000 participants in several studies, there was no association between this gene variant and blood pressure.

Overall, these findings indicate that SLCA9 is a high capacity urate transporter, and suggest that this protein plays an important part in controlling serum urate levels. They provide confirmation that common genetic variants in SLC2A9 affect serum urate levels to a marked degree, although they do not show exactly which genetic variant is responsible for increasing serum urate levels. They also provide important new insights into how the kidneys normally handle urate and suggest ways in which this essential process may sometimes go wrong. The findings could eventually lead to new treatments for gout and possibly for other diseases that are associated with increased serum urate levels.

Professor Mark Caulfield said: "This MRC funded study shows how a team of international researchers can find a completely unsuspected mechanism for urate handling in the kidney. Such discoveries could pave the way for new medicines."

Source: Queen Mary, University of London