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Study uncovers why anti-rejection drugs for transplant patients cause hypertension

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Modern medicine's ability to save lives through organ transplantation has been revolutionized by the development of drugs that prevent the human body from rejecting the transplanted organ.

But those antirejection drugs have their own side effects — sometimes serious.

A group of researchers led by scientists at Oregon Health & Science University has discovered the process that may be causing many of those side effects. And the discovery means those side effects likely can be dealt with cheaply and easily — with a class of widely used drugs that are often avoided in patients with organ transplants.

The researchers' findings were published this week in the online edition of the journal *Nature Medicine*.

The researchers examined the effects of a class of antirejection — or immunosuppressive — drugs called calcineurin inhibitors, which includes cyclosporine and tacrolimus.

Calcineurin inhibitors, which can be instrumental in preventing organ rejection in transplant patients, also can cause hypertension and kidney problems. The researchers' findings reveal what ultimately causes those problems — a calcineurin inhibitor spurs the production of an abnormally high level of a natural protein in the kidney.

Researchers found that a thiazide diuretic drug, which blocks the responsible protein, reduced hypertension in mice that had been given the calcineurin inhibitor. And mice lacking this protein did not develop hypertension at all.

The collaborative team of researchers, which included scientists from University College London, extended their observations to humans — kidney transplant patients in the United Kingdom.

University College London scientists found that kidney transplant patients who received the calcineurin inhibitor were more sensitive to a thiazide diuretic than were patients treated with other antirejection drugs.

The research results could mean very good news for transplant patients who have hypertension and potassium problems due to the antirejection drugs they're taking. That's because the drugs that can combat the elevation of the natural protein are generally the cheapest hypertensive drugs available — but many physicians have not been prescribing them for the side effects because they believed the problems were caused by changes outside the kidney.

"These findings should allow physicians to prescribe these simple drugs much more often and provide help to many, many more transplant patients who are suffering from these side effects," said David Ellison, M.D., head of OHSU's Division of Nephrology and Hypertension and the senior author of the study.

Ellison said the research points the way toward the next question he is planning to look at — taking a deeper look at the mechanism of how the antirejection drugs work. More research in that area might help scientists develop a drug that suppresses the body's attempt to reject a transplanted organ, but produces none of the hypertension and other side effects, he

said.

"That's my new grant proposal — to take it to the next step," Ellison said.

The lead investigators on the study were a nephrology trainee from Erasmus University in The Netherlands who worked for six months in Ellison's laboratory, and an honorary senior lecturer from UCL. Scientists from Charité University in Berlin, Germany, also contributed substantially.

"This was a great example of team science," Ellison said. "It was fun to have people from around the world collaborate to produce something that none of them was capable of producing alone."

Provided by Oregon Health & Science University