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A longer-living, healthier mouse that could hold clues to human aging

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A study by scientists at UCL (University College London) shows that mice lacking the insulin receptor substrate (IRS)-1 are more resistant to ageing than normal mice. The research adds to a growing body of work showing the importance of insulin signalling pathways as an ageing mechanism in mammals – and potentially humans.

The team studied 'knock-out' mice engineered to lack either insulin receptor substrate (IRS)-1 or -2. These proteins are activated by insulin, a hormone that regulates glucose and fat metabolism, informing the body's cells when the animal is well fed.

The study, published in The FASEB Journal, shows that mice lacking IRS-1 had an average lifespan increase of 20 per cent when compared to normal mice. In female mice lacking IRS-1 this figure was even higher, averaging 30 per cent. While the expected life-span for a mouse is about 25 months, one of the IRS-1deficient mice in this research lived for 38 months – 66 per cent longer than a normal mouse.

As well as living longer, the mice without IRS-1 also experienced better health than the normal mice as they aged – they had brighter eyes, were more alert and were much healthier overall. In comparison, the mice that lacked IRS-2 were shorter-lived than the normal mice and displayed signs of obesity and type 2 diabetes.

Professor Dominic Withers, who works with the UCL Centre for Research on Ageing and is lead author of the study, said: "Our

provisional results indicate that mice lacking IRS-1, particularly female mice, are more long-lived and show resistance to a range of markers that indicate ageing – including skin, bone, immune, and motor dysfunction.

“What’s more, these improvements were seen despite the fact that removing IRS-1 made the mice resistant to insulin throughout their lives. These results suggest that IRS-1 is a pathway conserved by evolution that regulates the lifespan of mammals, and it may point to methods of potentially delaying ageing in humans.

“We do not yet fully understand why lacking IRS-1 leads to longer life in mice. One possible explanation is that it makes them only mildly insulin resistant and that this, rather than having a negative effect on health, increases stress resistance, protects from damage and generally triggers other reactions in the body which extend life without compromising health.”

Dr David Gems, another of the study’s authors, added: “Other research has shown that mutations in single genes in the insulin pathway can extend the life of animals. However, our research adds new information because it shows that not only does manipulation of this pathway regulate how long animals live, it also shows that these effects allow the mice to stay healthier for longer. In these animals we see delay in the onset of age-related illnesses such as osteoporosis, diabetes and immune dysfunction. Obviously it’s much harder to study these mechanisms in humans because our life expectancy is so much longer, but this study and our other work on ageing are laying crucial scientific groundwork.”

The study follows other ageing research pioneered at the UCL Centre for Research on Ageing, led by Professor Linda Partridge. The teams at the Centre analyse the cellular and biochemical mechanisms of ageing in fruit flies, nematode worms and mice, and in particular the role of insulin signalling. Their work was recognised in June 2007 by a Strategic

Award from the Wellcome Trust totalling £5.1 million, to support their work examining what causes human bodies to age and decay. The UCL Institute of Healthy Ageing, incorporating the existing Centre, will be established in 2008 and will encourage further collaboration between UCL scientists working in this area.

Source: University College London