LETTER TO THE EDITOR

Insulin, food restriction and the extension of lifespan: the mechanism of longevity

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Dötsch *et al.* reported in this journal (1) on Blüher and co-worker's evaluation of the 18% increase in the lifespan of fat-specific insulin receptor knockout (FIRKO) mouse (2). As early as 3 months of age, these mice maintained a body weight approximately 20% below the body weight of their control littermates. The reduction in body weight was caused by an approximately 60% reduction of fat tissue. Interestingly, their appetite was not reduced, resulting in the food intake being equivalent to that of the control animals. As a consequence, food intake related to body weight exceeded that of the controls by more than 50% (3). The conclusion was that a reduction of fat mass without caloric restriction can be associated with increased longevity in mice, possibly through effects on insulin signalling.

Dötsch *et al.* highlighted that Blüher *et al.* fell short of explaining the mechanism of longevity in their FIRKO mice, because they speculated about a reduction in the generation of oxygen-free radicals (4, 5) or a mechanism involving insulin-like growth factor-I (IGF-I) signalling but unfortunately they did not provide any data regarding that hypothesis. We would like to mention here that a possible explanation of prolongation of lifespan by caloric restriction or defective insulin signalling has already been published (see ref. 6, Fig. 3): lower insulin levels or activity may increase autophagy and lysosomal proteolysis (7, 8), the anti-ageing cell repair mechanism which improves disposal of altered membranes and cellular organelles, and cell housekeeping (6, 9). This explanation is in line with recent genetic findings which demonstrate that autophagy genes are required for normal dauer morphogenesis and lifespan extension in *Caenorhabditis elegans* (10).

The good news is that the beneficial effect on longevity could be obtained by drugs, without any genetic manipulation: a decrease in free fatty acid (FFA) plasma levels by the lifelong administration of antilipolytic drugs to fasted rats may retard the age-related changes in biomarkers of ageing that are known to correlate with life expectancy (11, 12).

It is conceivable that in the FIRKO mice, the 50–70% reduction in fat mass throughout life might be associated with a decrease in the production and plasma levels of FFA.

The antilipolytic drug for the purpose of the Pharmacological Intensification of Suppression of Ageing (PISA) (this name was kindly suggested by Dr George

Martin, Seattle, WA, USA) is licensed for human use as a hypolipidaemic agent (Acipimox). From a practical point of view, the treatment might open a way to make more people likely to adhere to an anti-ageing regimen of dietary restriction otherwise too intensive to be endurable over an extended period involving much of human life (13).

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