PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Eating less to live longer

ArticleInfo		
ArticleID	:	4322
ArticleDOI	:	10.1186/gb-2002-3-3-reports0012
ArticleCitationID	:	reports0012
ArticleSequenceNumber	:	17
ArticleCategory	:	Paper report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2001–12–5 Received : 2001–12–5 OnlineDate : 2002–2–15
ArticleCopyright	:	BioMed Central Ltd2002
ArticleGrants	:	

ArticleContext	:	130593333

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Abstract

Restricting their intake of calories can further extend the lifespan of long-lived Ames dwarf mice

Significance and context

Ames dwarf mice live significantly longer than normal mice - their mean lifespan is extended by about 50% and their maximal lifespan by about 40%. These dwarf mice, which grow to approximately one-third the size of normal mice, are homozygous for the recessive *Prop-1*^{df} mutation. The *Prop-1* gene encodes a transcription factor that has a role in the embryonic development of the pituitary gland. Specifically, Prop-1 is required for proper differentiation of three cell types in the pituitary gland: somatotropes that produce growth hormones, lactotropes that produce prolactin and thyrotropes producing thyroid-stimulating hormone. As a consequence, Ames dwarf mice are deficient in these three hormones and, in addition, have very low levels of insulin-like growth factor 1 (IGF-1) in their bloodstream. Apart from being dwarf, *Prop-1*^{df} homozygotes are also infertile; the *Prop-1*^{df} mutation is therefore propagated by breeding heterozygotes.

Why do these mutant mice live longer than wild-type mice? It has long been suggested, on the basis of phenotypic similarities, that lifespan extension is conferred by mechanisms similar to those responsible for the extension observed under conditions of caloric restriction. This is a feeding regimen in which intake of calories is reduced while essential nutrients are provided at normal amounts. Reduced food intake has been shown to extend lifespan in such different organisms as nematodes and primates. The physiological and molecular basis of the phenomenon remains obscure, however.

Key results

Bartke and co-workers set out to investigate the proposed connection between the effects on longevity conferred by the *Prop-1*^{df} mutation and caloric restriction. Are Ames dwarf mice long-lived because they are under a 'genetically imposed' caloric restriction? If this were the case, one would expect that further physically restricting food intake would have little, if any, effect on their lifespan. If, on the other hand, the effects of *Prop-1*^{df} and those of caloric restriction on lifespan were the result of unrelated mechanisms, then reducing the food intake of Ames dwarf mice would further extend their lifespan.

This is exactly what Bartke and co-workers found. Ames dwarf mice kept under conditions of caloric restriction have significantly longer mean lifespan than either Ames dwarf mice fed *ad libitum* or wild-type mice kept under conditions of caloric restriction.

Conclusions

The additive effects of the *Prop-1*^{df} mutation and caloric restriction on lifespan suggest that the two work through different pathways to elicit their beneficial effects on longevity. There is also a qualitative difference in the effects of the *Prop-1*^{df} mutation and caloric restriction that further suggests unrelated mechanisms: caloric restriction appears to reduce the pace of the aging process, whereas the *Prop-1*^{df} mutation delays the appearance of signs of aging. After the onset of these signs, aging-related decline and deterioration proceed at wild-type rates.

Reporter's comments

With this simple analysis, the authors address the hypothesized link between the effects of the *Prop-1*^{df} mutation and caloric restriction. Given the commonalities between Ames dwarf mice and animals grown under caloric restriction, such as smaller body size and lower levels of insulin and insulin-like growth factor (IGF-1) in their bloodstream, it is surprising that different mechanisms mediate the effects on longevity. These similarities could nevertheless indicate a common component of lifespan extension. As the authors note, insulin and IGF-1 signaling have been implicated in regulating the lifespan of several other model organisms, indicating the operation of an evolutionarily conserved process. What are the constituents of this process? We are only now beginning to confront this question. We also have little understanding of how, at the molecular level, caloric restriction eventually leads to lifespan extension. Obviously, both the *Prop-1*^{df} mutation and caloric restriction somehow alter cellular physiology in a way that allows longer life. Describing this altered physiological state and understanding the molecular mechanisms that bring it about will not only shed light on the phenomenon of aging but should also inspire interventions that, by mimicking or attaining this state, might have substantially beneficial effects on longevity.

Table of links

Nature

References

1. Bartke A, Wright JC, Mattison JA, Ingram DK, Miller RA, Roth GS: Extending the lifespan of long-lived mice. Nature. 2001, 414: 412-. 0028-0836