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Pituitary removal in adult mice increases life span

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Abstract

Dwarf mutations reduce levels of pituitary hormones and increase life span in mice. But because these dwarf mutations confer life-long hormone deficits that alter development and dramatically reduce fecundity, the relevance of these models to normal aging has been questioned. We examined effects of pituitary hormone withdrawal at different ages using hypophysectomy (surgical removal of the pituitary). Hypophysectomy at 1 month of age extended life span significantly (15%), but hypophysectomy at 9 months of age extended life span to the greatest magnitude (21%) of any age we tested. These results demonstrate pituitary hormone withdrawal can extend life span even if these hormones are removed relatively late in life.

Keywords: Nutrients; Hypophysectomy; Pituitary; Life span; Aging; Mammal; Mice, Mouse; Calorie restriction; Insulin; IGF-1; Thyroid hormone; Dwarf; Snell; Ames

Hypophysectomy (surgical removal of the pituitary) dramatically reduces levels of circulating growth hormone (GH), insulin-like growth factor-1 (IGF-1), and thyroid hormones, as well as other pituitary hormones. Additionally, hypophysectomy has been shown to delay many biomarkers of aging, and has been linked to slight life span increase in rats (Everitt et al., 1980). To a large extent, the effects of hypophysectomy are similar to the effects of the Snell and Ames dwarf mutations in mice, which also very severely reduce the circulating levels of GH, IGF-1, and thyroid hormones (Flurkey et al., 2001; Bartke et al., 2001). Dwarf mice out-live normal controls and dwarfs exhibit many forestalled phenotypes of aging (Flurkey et al., 2001; Bartke et al., 2001). But because dwarf mutations confer lifelong hormonal deficits that slow growth, alter development and prevent reproduction, the relationship of these models to normal mammalian aging has been questioned (Carter et al., 2002; Sonntag and Ramsey, 2002). Furthermore, if dwarf mutations cause life span extension that is dependent on developmental abnormalities (especially at the expense of reproduction), clinical relevance of these models is limited. In dwarf mice the interplay between timing of hormone withdrawal and aging is difficult to assess; however, hypophysectomy can be used to examine post-developmental withdrawal of pituitary hormones.

In order to study the effect of pituitary hormone withdrawal at various ages, we hypophysectomized male mice at ages ranging from before sexual maturity (0.75 months) to late middle age (15 months) and replaced only corticosterone (Supplemental materials). Mice hypophysectomized at 0.75 months after birth showed no increase in life span, but mice undergoing the surgery at 1 month of age had a 15% increase in mean life span ($P < 0.002$), and those hypophysectomized at 9 months had a 21% increase ($P < 0.002$), relative to controls (Fig. 1 and Table 1). Maximum life span (oldest 20% of the population) was comparably extended in these hypophysectomized groups (Table 1). Importantly, these results show that pituitary hormone withdrawal well into mature adulthood can dramatically extend life span. Thus, hypophysectomy of normal mice during adulthood must affect some fundamental aging process and need not produce maturational abnormalities (as seen in the dwarf mice) in order to result in life extension. Similar to dwarf mice, hypophysectomized mice eat less than controls on a per gram body weight basis (our unpublished data), which implies that at least part of the life span extension may be due to a mechanism related to caloric restriction.

As with many interventions that increase life span, hypophysectomy produces drawbacks as well as benefits.

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Table 1
Mean and maximal life span of mice hypophysectomized at various ages + S.E.M

Group	Mean LS	Maximum LS	*P*-value vs. control (complete LS)	*P*-value vs. control (maximum LS)	*N*
HX 0.75 month	865 ± 40	1047 ± 32	NS	NS	15
HX 1 month	971 ± 21	1162 ± 32	0.002	0.001	39
HX 9 months	1030 ± 33	1175 ± 4	0.002	0.005	13
HX 11 months	924 ± 16	1004 ± 18	NS	NS	15
HX 12 months	886 ± 14	941 ± 14	NS	NS	12
HX 15 months	812 ± 22	954 ± 32	NS	NS	23
Controls	848 ± 18	1026 ± 13	–	–	70

The life spans of the longest-lived 20% of animals were used to calculate maximum life span. HX = hypophysectomized, NS = not significant. P values were corrected for multiple comparisons.

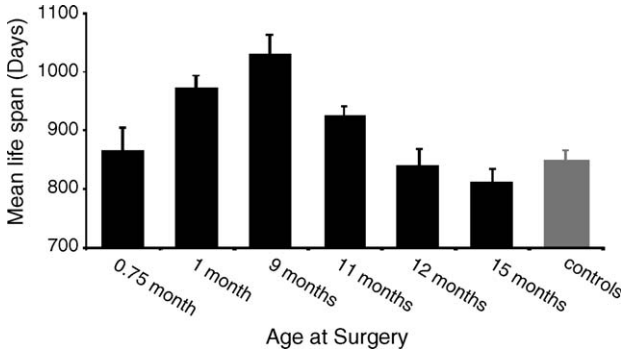

Fig. 1. Pituitary hormone withdrawal during adulthood extends life span in mice. The mean life span extension benefit was 15% in mice undergoing pituitary removal at 1 month of age ($P < 0.002$), and 21% in mice undergoing pituitary removal at 9 months of age ($P < 0.002$) vs. control animals. Mean life spans ± S.E.M.

Hypophysectomy at 0.75 months of age produces an impairment, probably developmental, that prevents the extension of life span. Conversely, when this procedure is performed after 9 months, the maximal life span benefit for pituitary removal has passed, and life span is limited by early-life pituitary function (Fig. 1). We note that the life span-extending mechanism of hypophysectomy is unlikely to be due simply to endocrine withdrawal during senescence, as might be seen, for example, if the effect resulted from removing support for endocrine-dependent tumors. Hypophysectomy after 9 months misses a critical period during which a pituitary hormone(s) must be withdrawn to increase life span.

Our results are the first example of life span extension by hypophysectomy in mice, and demonstrate that hypophysectomy can significantly extend life span even if conducted surprisingly late in life. Our results are also in agreement with studies in rats that show hypophysectomy at 2 months of age slows many biomarkers of aging, but when conducted at 13 months of age, hypophysectomy has limited benefit (Everitt et al., 1980).

In addition, the life span extension we observe parallels RNA interference (RNAi) studies of the insulin-like peptide receptor *daf-2* in *C. elegans*. These studies demonstrated a maximal life span benefit when *daf-2* expression was diminished in the young adult, with the benefit tapering when RNAi was initiated later in life (Dillin et al., 2002). The similarity of these results in nematodes and mammals may mean that endocrine function operates during mature adulthood to set life span potential in a wide range of species and this study contributes to a growing body of research that suggests that evolutionarily conserved nutrient-responsive signaling pathways may be a promising target for interventions that delay human aging (Powers et al., 2006).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.mad.2006.03.003.

References

Bartke, A., et al., 2001. Exp. Gerontol. 36, 21–28.
Carter, C.S., Ramsey, M.M., Sonntag, W.E., 2002. Trends Genet. 18, 295–301.
Dillin, A., Crawford, D.K., Kenyon, C., 2002. Science 298, 830–834.
Everitt, A.V., Seedsman, N.J., Jones, F., 1980. Mech. Ageing Dev. 12, 161–172.
Flurkey, K., Papaconstantinou, J., Miller, R.A., Harrison, D.E., 2001. Proc. Natl. Acad. Sci. 98, 6736–6741.
Powers RW III, Kaeberlein M, Caldwell SD, Kennedy BK, Fields S. Extension of chronological life span in yeast by decreased TOR pathway signaling. Genes Dev. 2006;20(2):174–84.
Sonntag, W.E., Ramsey, M.M., 2002. Sci. Aging Knowl. Environ. 2002, 17.