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Opinion

Food restriction, pituitary hormones and ageing

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Abstract

Reducing the intake of food in rodents inhibits body growth, retards most physiological ageing processes, delays the onset of pathology and prolongs life. Food restriction (FR) reduces pituitary hormone secretion and in consequence has been called 'functional hypophysectomy'. Direct life-long comparisons in the rat showed that hypophysectomy (HYP) (a complete absence of pituitary hormones) has a greater anti-ageing action than FR (a partial lack of pituitary hormones) on collagen, kidney and muscle. This suggests that pituitary hormones accelerate ageing. Recent American research on genetic variants of the mouse indicates that pituitary growth hormone (GH) may accelerate ageing and shorten life. Both the Snell and Ames dwarf mice have a deficiency of pituitary GH and live 50% longer than normal mice. The Snell dwarf mouse has retarded ageing of both collagen and immune functions. The Ames dwarf mouse has high antioxidant enzyme activities in liver and kidney. A transgenic human GH mouse is short lived, has a low activity of antioxidant enzymes in liver and kidney and an early development of disease in these organs. It is postulated that FR by reducing the secretion of pituitary hormones, such as GH, diminishes the oxidative damage of certain tissues, thereby delaying the development of age-related diseases in these tissues and by this means extends life.

Abbreviations: FR – food restriction, food restricted; GH – growth hormone; HYP – hypophysectomy, hypophysectomised

Introduction

It is well established that long-term reduction of food intake retards ageing in many animal species (Masoro 2001). There is a much smaller literature showing that HYP in young rodents also retards ageing in many tissues (Everitt and Meites 1989). It is the opinion of this author that these two effects are strongly linked.

FR and ageing

When the food intake of a rat is reduced by about 40% without malnutrition from weaning until old age, body growth is inhibited, almost all physiological ageing processes are retarded, the onset of most pathological processes is delayed and the maximum life duration is extended by 40% or more (for reviews see Weindruch and Walford 1988a; Masoro 2001). The classical finding of McCay et al. (1935) that lifespan is increased by FR has been confirmed in many laboratories around the world and has been demonstrated in rats, mice, hamsters, fish, worms and fruit flies. The anti-ageing effect of FR has also been demonstrated in the rhesus monkey (Roth et al. 2001) and in Japanese living on the island of Okinawa, who eat 20% less food than those in Tokyo (Akisaka et al. 1996). Recent studies (Turturro et al. 1999) on

four genotypes of mice and three genotypes of rats showed that 40% reduction in food intake had similar life extending effects in both males and females of the seven genotypes. The major dietary factor that determines survival in the rat is the calorie intake (Masoro 1995).

FR reduces the fertility of animals. Holliday (1989) proposed that the anti-ageing action of FR may have evolved in nature in response to periods of food deprivation. At such times resources would be diverted from reproduction to maintenance of the adult body and thereby increase survival.

FR compared with HYP

Possible mechanisms of the anti-ageing and life-prolonging actions of FR have been reviewed by Masoro (2001). A longstanding hypothesis is that the anti-ageing actions of FR are mediated by hormones (Everitt et al. 1980; Meites 1989; Han et al. 1998; Mobbs et al. 2001). For many years FR has been called a 'functional HYP', because reduced pituitary hormone levels in blood are observed in FR animals (Mulinos and Pomerantz 1940; Campbell et al. 1977; Armario et al. 1987; Herlihy et al. 1990; Gautsch et al. 1998). The secretion of almost all hormones is suppressed by FR except for corticosterone (Han et al. 2001). Meites (1989) suggested that FR changes neurotransmitter metabolism in the hypothalamus, thereby decreasing the secretion of hypothalamic releasing hormones and so diminishing pituitary hormone secretion.

Long-term HYP, like FR in rats and mice, has been shown by a number of investigators to inhibit age-related changes in many functions including the immune system, blood vessels, metabolism, collagen, kidney, muscle, ovary, adrenal cortex, etc. (for reviews see Weindruch and Walford 1988b; Everitt and Meites 1989). It must not be forgotten that HYP causes a fall in food intake (Everitt et al. 1980). Weindruch and Walford (1988b) have suggested that the reduced rate of ageing of HYP rats may be due to their low food intake, rather than their lack of pituitary hormones.

Some thirty years ago at the University of Sydney we began our longitudinal research directly comparing the anti-ageing effects of FR and HYP in conventional male Wistar rats consuming the same amount of food. Commencing at age 60 to 70 days, we compared ageing parameters over the lifespan in normal ad libitum fed controls with FR rats (secreting low levels of pituitary hormones) and HYP rats (secreting no pituitary hormones) on the same food intake (Table 1, Everitt 1971; Everitt et al. 1980; Everitt and Wyndham 1982). It was found that collagen fibres taken from the tail of HYP rats aged at about half the rate of the ad libitum fed controls, with FR rats ageing at an intermediate rate (Everitt 1971 and 1976). FR rats aged at a faster rate than HYP rats even though they ate the same amount of food. It is believed that pituitary hormones secreted by FR rats are increasing the ageing rate of their collagen fibres. Similarly, it was also found that HYP had a greater anti-ageing action than FR on the age-related thickening of the kidney glomerular basement membrane (Wyndham et al. 1987). Furthermore, when we examined age changes in the variation of fibre size in the soleus muscle of the old rat, HYP had a greater inhibitory action than FR (Shorey et al. 1993). In our opinion, FR rats age faster than HYP rats, when eating the same amount of food, because they secrete pituitary hormones which increase their ageing rate (Everitt and Meites 1989).

HYP also has a greater inhibitory effect than FR on the development of pathology in old age (Table 1, Everitt and Meites 1989). From our pathology records collected over 25 years, we calculated the frequency of gross pathology at autopsy in old rats dying at ages greater than 800 days (26 months). Gross pathology consisted of lung lesions, enlarged hearts and kidneys, plus tumours and haemorrhages and was seen in 100% of controls, but only 74% of FR rats and 48% of HYP rats. Likewise, gross tumour frequency at autopsy in old rats was reduced to a greater extent in HYP than in FR rats (Table 1, Everitt and Meites 1989). Thus

Table 1. Direct comparison of the anti-ageing effects in hypophysectomised (HYP) and food restricted (FR) rats on the same food intake. The studies commenced when young at age 60–70 days (2 months) and ageing parameters are compared here in old age at 800+ days (26+ months) in male Wistar rats.

Parameters	Control	FR	HYP	Reference
Collagen fibre break time (min)	225	105	75	Everitt 1971, 1976
Kidney membrane thickness (nm)	632	392	296	Wyndham et al. 1987
Soleus fibre size variation (%)	29	20	12	Shorey et al. 1993
Rats with gross pathology (%)	100	74	48	Everitt and Meites 1989
Rats with gross tumours (%)	67	34	12	Everitt and Meites 1989

HYP had a greater inhibitory effect than FR on the development of age-related pathology.

From lifespan data collected over 25 years, the maximum life duration of ad libitum fed rats was 1201 days (40 months). The maximum life duration of FR rats was 1515 days (50 months), a 25% increase. For HYP rats receiving low dose cortisone therapy the maximum was 1353 days (45 months) (Everitt and Meites 1989). Untreated HYP rats survived to a maximum of only 910 days. Obviously some pituitary hormones, such as adrenocorticotrophic hormone which stimulates the secretion of adrenocortical hormones, such as corticosterone in the rat, are necessary for normal survival. In our research a complete absence of pituitary hormones led to the slowest rate of ageing, but reduced the maximum life duration. Weindruch and Walford (1988b) believe that this failure of HYP to extend the species-specific maximum lifespan in these rats is a serious flaw in the pituitary theory of the action of dietary restriction. However, genetic dwarf mice with severe pituitary hormone deficiencies, discussed in the next section, have both retarded ageing and extension of the maximum lifespan by about 50% (Bartke et al. 2001; Flurkey et al. 2001). It must be emphasised that these mice are secreting low levels of pituitary and target gland hormones and have a low food intake (Bartke et al. 2001).

Hormones and ageing. Possible role of oxygen free radical damage

In recent years there has been a lot of interest in genetic variants of the mouse in relation to pituitary hormone secretion and life duration. A single-gene mutation which reduces pituitary hormone secretion can extend the life of the mouse by 40% (Flurkey et al. 2001) There are two genetic dwarf mice, the Ames and Snell mice with different gene mutations causing deficiencies of pituitary hormones and increased life span (Bartke et al. 2001). The Snell mouse with a recessive mutation at the Pit 1 dw locus on chromosome 16 has retarded ageing of collagen and six immune functions, plus a long life (Flurkey et el. 2001). The Ames dwarf mouse with a closely related recessive mutation at the Prop 1 df locus on chromosome 11 has deficiencies of pituitary GH, prolactin, thyroid stimulating hormone and secondary hormones (Bartke et al. 2001). The Snell and Ames dwarf mice have reduced food intake, body growth, fertility, body temperature and blood glucose (Bartke et al. 2001), changes also seen in FR and HYP rodents (Everitt and Meites 1989). A high activity of two antioxidant enzymes, catalase and Cu-Zn superoxide dismutase has been found in the liver and kidney of the Ames dwarf mouse, as well as evidence of reduced oxidative damage (Hauck and Bartke 2001). Thus the long life of these mice is associated with a high activity of antioxidant enzymes and less oxidative damage in certain tissues.

Antioxidants are believed to protect cells from the damaging actions of oxygen free radicals (Sohal and Weindruch 1996). Oxidative stress is implicated in the pathogenesis of many diseases and thereby becomes a determinant of life expectancy (Sohal and Weindruch 1996; Yu 1996). Oxygen free radicals generated during the metabolism of food are toxic, causing damage to DNA bases, lipids and proteins (Sohal and Weindruch 1996; Yu 1996) and these changes are attenuated by food restriction (Yu 1996). A number of studies have related ageing biomarkers and life duration to the activity of free radical scavengers, such as antioxidant enzymes in liver, kidney and other organs (Hauck and Bartke 2001), and also to blood levels of antioxidants, such as vitamin C, uric acid, carotenoids and glutathione (Short et al. 1997).

Both nutrition (Gong et al. 1997) and hormones (Bolzan et al. 1995) are reported to affect antioxidant activity in tissues, but some inconsistencies exist (Gomi and Matsuo 1998; Masoro 2001). The work of Rao et al. (1990) showed that the activity of liver Cu-Zn superoxide dismutase in the rat falls progressively with age and that food restriction slows the decline. As we have seen, pituitary hormones affect antioxidant enzyme production. Hauck and Bartke (2001) studied a transgenic mouse overexpressing GH, which reduced the activity of antioxidant enzymes in liver and kidney. In these mice blood GH levels were high, body growth was doubled and life duration was shortened, due to the early development of liver tumours and kidney disease. Thus an excess of GH compromised free radical defences, leading to the early onset of disease which shortened the life of these mice.

Conclusion

It is believed that the anti-ageing and life-prolonging actions of FR may be mediated by the pituitary hormones and the antioxidant enzymes. FR by reducing pituitary hormone secretion may increase antioxidant defences, which inhibit the development of age-associated pathology and thereby extend life.

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