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Nutrition, hormones and aging

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Nutrition, Hormones and Aging*

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The rate of aging in the laboratory rat can be slowed by food restriction begun just after puberty (70 days) or by removal of the pituitary gland at the same age. These two procedures retard the rate of aging in the collagen fibres of rat tail tendon and inhibit the thickening of the capillary basement membrane in the kidney glomerulus. Both food restriction and hypophysectomy inhibit the development of age associated diseases such as renal disease, hind leg paralysis and tumours. The anti-aging action of hypophysectomy is greater than that of food restriction in rats eating the same amount of food per day. The maximum life duration of the male Wistar rat is 1201 days and this is extended to 1335 days in hypophysectomized rats and 1525 days in food restricted rats. Most pituitary hormones and hormones of the thyroid, adrenal cortex and testis have been shown to affect the rate of aging in many tissues. The rate of collagen aging is determined mainly by the energy content of the diet, while the development of age associated renal disease is influenced by both energy and protein intake. It is postulated that centres in the brain such as the hypothalamus time the rate of aging and the development of age-related disease by modulating food intake and pituitary hormone secretion.

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ผลจากการทดลองในหนูพบว่าอัตราการเกิดความชราภาพจะลดลงด้วยการจำกัดอาหารหรือการตัดต่อมใต้สมอง โดยเริ่มจากวัยที่สามารถผสมพันธุ์ได้ (อายุ 70 วัน) วิธีการทั้งสองดังกล่าวจะลดความเสื่อมของ collagen fibre ที่เอ็นของหางหนู ยับยั้งการหนาตัวของ capillary basement membrane ที่ไต อัมพาตของขาหลังและการเกิดก้อนเนื้อทูม การตัดต่อมใต้สมองจะมีผลในการชลอความแก่ได้มากกว่าการอดอาหารในหนูที่ได้จำกัดปริมาณอาหารต่อวัยเท่ากับปริมาณอาหารต่อวันเท่ากัน หนูจะมีอายุสูงสุด 1201 วัน แต่เมื่อตัดต่อมใต้สมองจะมีอายุ 1335 วัน และเมื่อจำกัดอาหารจะมีอายุ 1525 วัน

ฮอร์โมนจากต่อมใต้สมอง ฮอร์โมนจากต่อมไทรอยด์ ต่อมหมวกไตและอัณฑะมีผลต่ออัตราความชราภาพของเนื้อเยื่อต่าง ๆ การจำกัดพลังงานจากอาหารจะชลอสภาพความแก่ใน collagen fibre และการจำกัดพลังงานจากอาหารและปริมาณโปรตีนจะชลอการเกิดโรคไตในวัยชรา

คาดกันว่ามีศูนย์ในสมอง เช่น hypothalamus ในการกำหนดอัตราการเกิดความชราภาพ และการเกิดโรคในวัยชรา โดยควบคุมการรับประทานอาหารและการหลั่งของฮอร์โมนจากต่อมใต้สมอง

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* Lecture delivered at Chulalongkorn University Hospital on 27 June 1984.

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Due to the rising numbers of the elderly in the population aging is becoming a major medical and social problem not only in Western countries like Australia, but also in Asia. The percentage of the aged over 65 years is 10% in Australia and 5% in certain Asian countries such as Thailand and India. These numbers are continuing to rise and in Australia the numbers of the very old (those over 75 years) will double in the next 25 years. It is the very old who have most of the medical and social problems.

There are two main reasons for the increasing numbers of the aged in our population. First, the successful control over the killer diseases (mainly infectious diseases) of the young and middle aged enables more of the population to survive to old age. Second, successful birth control measures directly reduce the percentage of young people in the population. Thus the medical and social problems of the aged are developing due to these advances in medical science.

The ultimate basis of the medical and social problems of the elderly is to be found in the biological breakdown of the body in old age. If we did not grow old there would be no medical or social problems associated with aging. This then is the reason for endeavouring to understand the biology of aging.

Biological Aging

An old person can be recognized immediately by the obvious wrinkling of the skin of the face and hands, compared with the wrinkle-free skin of the baby or child. Another obvious age change is the reduced capacity for doing strenuous physical work. The young adult of 30 years returning from a holiday can race up a flight of stairs carrying his 20kg of luggage, but the 80 year old can do this only very slowly even when healthy.

The life cycle begins with conception and is followed successively by embryological development and growth, birth, growth during childhood, sexual maturation at puberty, and the attainment of maximal development of most body functions by age 25 years in man. This is followed by the decline or degenerative phase which we call aging. Biological aging is characterized by two changes, the physiological decline and the development of age-associated disease. Many body functions undergo a 1% decline per year between ages 30 and 80 years. Thus the vital capacity of the lungs, renal blood flow and glomerular filtration rate and the capacity for intense physical work of the 80 year old are only 50% of the corresponding function in the 30 year old. Concurrent with the physiological decline is the development of age-related pathology. Autopsies in old age show the presence of multiple pathology.[1] The average number of lesions rises from 4 in the 60 year olds to 12 in the 90 year olds.[2] The age related rise in the incidence of pathology may also be seen in the frequency of abnormal results in routine tests of blood picture, blood pressure, electrocardiogram, liver function tests, glucose tolerance, kidney function tests, visual acuity, auditory acuity, etc. In the 30 year old one out of 20 tests may be abnormal but in the 80 year old this may have risen to 8 abnormal tests.[3]

Slowing The Aging Process By Food Restriction

It is possible in the rat to retard

the rate of aging and prolong life by food restriction. The classical studies of McCay and colleagues[4] showed that moderate food restriction begun after weaning refood restriction begun after weaning retarded growth and prolonged life by up to 50% in the laboratory rat. This has been confirmed repeatedly in many laboratories around the world, not only for the rat, but also for the mouse, fish and a number of invertebrates. Food restriction prolongs life because it delays the onset of the diseases of old age.[5] In addition, food restriction retards the rate of physiological aging of collagen fibres in the rat tail tendon.[6]

Food restriction inhibits the secretion of most pituitary hormones.[7] This observation raises the question : Is the anti-aging of food restriction due to the lack of a dietary factor or to the lack of a pituitary factor? It was postulated that food restriction inhibits the secretion of a pituitary aging factor.[8]

Retarded Aging Of Hypophysectomized Rats

The pituitary gland or hypophysis is a small gland at the base of the brain in the rat. This gland secretes about 10 hormones which directly or indirectly affect the functions of almost every cell in the body. The pituitary can be removed by placing the anaesthetized rat in a stereotaxic apparatus, inserting a hypodermic needle through the external auditory canal into the pituitary and withdrawing the gland by suction.[9] Within a few days of operation the food intake stabilizes at 7 g per day or 50% of the intake just before operation at 70 days (15 g per day) or 40% of the ad libitum food intake of the adult male rat (19 g per day). We compared the physiological aging, the development of age-associated diseases and life duration in three group of rats : ad libitum fed controls, hypophysectomized rats and food restricted intact rats eating the same amount of food (7 g per day) as hypophysectomized rats.[10] Animals used in this study were conventional male outbred Wistar rats housed in an air conditioned animal room at 27° C, 50-70% relative humidity and 12 hours of artificial light. In intact controls body weight increased during growth reaching a maximum of about 500 g at middle age at 500 days, whereas maximum weight was less than 200 g in both hypophysectomized and food restricted rats.

Collagen Aging

The most widely used test of physiological aging in the rat utilises collagen fibres from tail tendon. A bundle of fibres is removed with forceps from the anaesthetized rat after making an incision near the tip of the tail. Individual fibres are teased apart and tested in vitro. We measure the time it takes a load of 2 g to break an isolated fibre when immersed in 7M urea solution at 40° C.[11] The breaking time is measured by an electric clock started and stopped with a micro switch. Collagen fibres from the young rat just before operation at 70 days break in about 1 minute. The breaking time rises progressively with age taking about 60 minutes in rats aged 400 days and 200 minutes at 800 days. In rats hypophysectomized at age 70 days the rate of collagen aging is halved and in food restricted rats the aging rate is about 70% of that of ad libitum fed controls (Fig. 1)

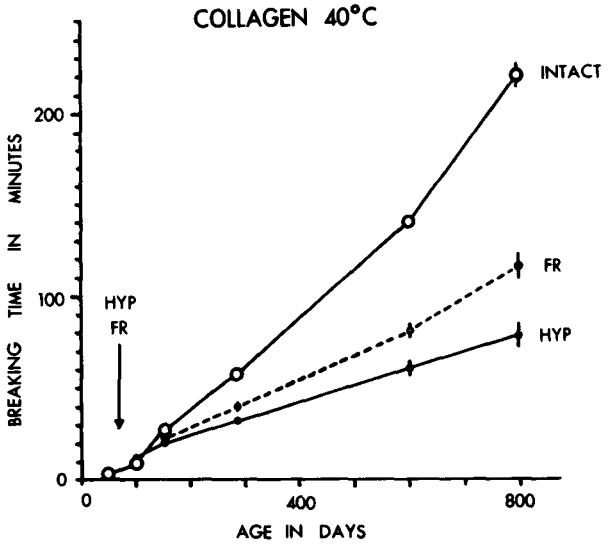

Fig. 1 The inhibitory actions of hypophysectomy (HYP) and food restriction (FR) on the aging of collagen fibres in rat tail tendon. Adapted from Everitt AV. Proc Aust Assoc Gerontology 1971; 1 : 127-132.

Body Temperature

In cold blooded animals body temperature is a determinant of the rate of aging, but in mammals this temperature-aging relationship has not been clearly established. In the present study deep body (rectal) temperature did not change with age and was not affected significantly by hypophysectomy or food restriction. However, tail temperature was affected by age and by treatment. In intact ad libitum-fed rats tail temperature declined during the first year of life. Tail temperatures of both food restricted and hypophysectomized rats were lower than intact ad libitum fed rats.[12] Since low tail temperatures were found in rats with lower rates of collagen fibre aging, this suggests that tail temperature is a determinant of tail tendon collagen aging.

Renal Disease and Renal Aging

The development of age-associated renal disease in the rat may be monitored by measuring the excretion of total protein in urine.[13] Protein excretion rises progressively with age from about 1 mg per day in young rats aged 100 days to 20 mg per day in old rats 1000 days. There is no rise in protein excretion with age in either food restricted or hypophysectomized rats.[4] The level of protein excretion parallels the incidence and severity of renal histopathology. In the old control rat kidney there is increased PAS (periodic acid Schiff) stained material in the glomerulus indicating thickened basement membranes and proliferation of the mesangium. The percentage of abnormal glomeruli rise from 36% in young rats at 100 days to 81% at 1000 days, but remains low in old food restricted rats (24%) and old hypophysectmized rats (14%) at 1000 days. There is also a large age associated rise in the number of pro-

teinaceous casts from 0.03 cast/mm^2 at 100 days to 2.18 casts/mm^2 at 1000 days. There is no significant age change in cast count in food restricted or hypophysectomized rats.

Thus food restriction and hypophysectomy prevent the development of age-associated renal histopathology. Renal aging may be measured by the thickness of the basal lamina of the capillary loop in the glomerulus which increases linearly with age from 250 nm at 100 days to 1200 nm at 1000 days.[13] The slope of the regression line is halved by hypophysectomy and is 70% of the control value in food restricted rats (Fig.2). Thus the

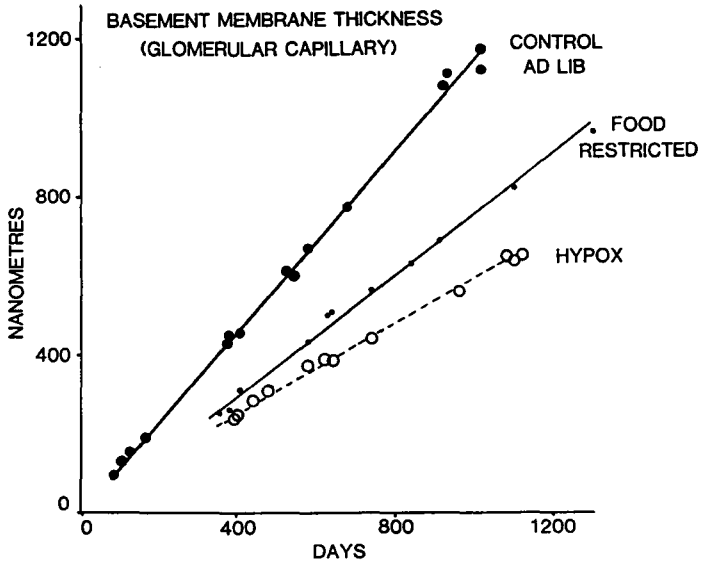

Fig. 2 The anti-aging actions of hypophysectomy and food restriction on the age-related thickening of the basal lamina of the glomerular capillaries in the rat kidney.

anti-aging actions of hypophysectomy and food restriction on basement membrane thickening are almost the same as those on collagen fibre breaking time.

Hind Leg Paralysis

The development of hind leg paralysis is also inhibited by hypophysectomy and food restriction.[15] In this disease the old rat is unable to use its hind legs and so propels itself forward by means of its fore limbs. In rats 1000 days or more the disease is found in 35% of intact ad libitum fed controls, 6% of food restrictd rats and 0% of hypophysectomized rats. In observations over 20 years the disease has not been seen in any hypophysectomized rat up to the age of 1325 days (41 months). Histological examination of hind leg muscle shows the presence of degenerative changes associated with the loss of the normal muscle banding pattern in old controls. Such changes are of very rare occurrence in old hypophysectomized and food restricted rats.

Other Gross Pathology

With increasing age there is progressive enlargement of heart ventricles (in the absence of hypertension) and thickening of the media of the thoracicaorta,[10] These age related changes develop more slowly in hypophysectomized and food restrictd rats. Internal haemorrhage into the thoracic cavity is seen in 15% of controls, 16% of food restricted and 12% of hypophysectomized rats.

Gross tumours are seen at autopsy in 67% of old ad libitum fed control rats aged 800 days or more. About half of the tumours are in endocrine organs and half in various other organs. The tumour incidence is lower in hypophysectomized rats (12%) and food restricted rats (34%).

Gross pathology at autopsy is seen in all old ad libitum fed controls aged 800 days or more, compared with 62% of food restricted and 48% of hypophysectomized rats.

Life Duration

The mean life duration of untreated hypophysectomized rats is about 500 days compared with 750 days in intact ad libitum fed controls. However if hypophysectomized rats receive a weekly subcutaneous injection of cortisone their life is prolonged significantly to mean of 925 days compared with 858 days in food restricted rats and 785 days in the ad libitum fed controls.[10] Maximum life durations over a period of 28 years are 1201 days for ad libitum fed controls, 1525 days for food restricted rats and 1335 days for hypophysectomized rats.[9]

Conclusion

Both food restriction and hypophysectomy retard physiological aging of collagen fibres in tail tendon and the age associated thickening of the basement membrane (basal lamina) in the glomerular capillaries of the kidney. Similarly food restriction and hypophysectomy inhibit the development of kidney disease, hind leg paralysis and tumours. In all of these tissues hypophysectomy has a greater antiaging action than food restriction.

Hypophysectomy and Food Restriction in Middle Age

Surgical removal of the pituitary from the middle aged rat at 400 days, like food restriction begun at the same age, also retards the aging of collagen fibres in tail tendon.[10] However, hypophysectomy at 70 days has a greater antiaging action than hypophysectomy at 400 days.

The age-related rise in urinary protein excretion is reversed after hypophysectomy at 400 days. One year after operation protein excretion approximates that of the young rat. Thus the development of age-related renal disease is not only halted but reversed by hypophysectomy in middle age.[10]

Raised Food Intake in Hypophysectomized Rats

A lesion in the ventromedial nucleus of the hypothalamus will double the food intake (from 7 g to 15 g per day) of the hypophysectomized rat which becomes abese.[14] In such fat hypophysectomized rats the abdominal fat depots (retroperitoneal and epididymal fat pads) are 3 times heavier on a body weight basis than those in lean hypophysectomized and intact controls. Does the raised food intake accelerate the development of age associated renal disease and increase the rate of collagen aging?

Protein excretion in fat hypophysectomized rats eating 15 g food per day was not significantly different from that in lean hypophysectomized rats eating 7 g per day. However, the same increase in food intake in intact rats significantly elevated protein excretion and increased the incidence of renal glomerulopathy in old age.[14] Thus the 'aging' effect of food on proteinuria development and renal pathology onset occurred only if the pituitary gland was present.

The pituitary-dependent aging effect of food could not be demonstrated on collagen fibre aging.[14] In both hypophysectomized rats and food restricted rats the rate of collagen aging was the same whether they ate 7 g or 15 g of food per day. However, collagen fibre aging was significantly greater in intact food restricted rats than in hypophysectomized rats eating the same amount of food. This indicates that pituitary hormones have an aging action on collagen fibres.

Hormonal Factors in Aging

Hypophysectomy clearly inhibits the development of age-associated pathology such as renal disease, hind leg paralysis and tumours and also retards the aging of collagen fibres and basement membranes of glomerular capillaries. Thus pituitary hormones must in some way be accelerating these aging processes. The pituitardy gland secretes about ten hormones, many of which have been shown to affect one or other age related process.[16] Thyroidectomy, like hypophysectomy, inhibits the development of age associated proteinuria and also retards collagen aging in tail tendon.[17] Thyroxine replacement therapy restores proteinuria development and collagen aging to the level in the intact rat of the same age. Thyroxine injections in the intact rat accelerate the aging of collagen fibres in tail tendon, elevate urinary protein excretion and increase the incidence of age associated renal lesions. Growth hormone accelerates the development of age-related proteinuria and renal histopathology in hypophysectomized rats and has a mild inhibitory action on collagen aging.[16] Cortisone injections accelerate collagen aging in hypophysectomized rats, and have a mild inhibitory action on the development of age-related proteinuria.[16] Castration of the male rat slows the aging of collagen fibres and inhibits the development of age asociated proteinuria.

Dietary Factors in Aging

We investigated the role of total food intake in aging in 4 groups of rats fed respectively 75 (ad libitum intake), 50, 25 and 12.5 kcal per day.[6] The maximum body weights were directly proportional to food intake and were approximately 450, 300, 150 and 75 g for the respective groups.

Life Duration

Of the 4 groups the longest lived were the mildly restricted rats eating 50 kcal per day with a mean survival of 936 + 29 days, compared with 728 $\pm$ 46 days in the ad libitum fed group eating 75 kcal per day.[18] The most severely food restricted group (12.5 kcal per day) had a significantly reduced life duration of 296 $\pm$ 43 days, while the moderately restricted group (25 kcal per day) lived 859 $\pm$ 38 days.

Collagen Aging and Age Associated Renal Disease

All 3 food restricted groups (12.5

25 and 50 kcal per day) had significantly lower rates of collagen fibre-aging compared with the ad libitum fed group.[6] However, there was no significant difference between food restricted groups suggesting that the faster aging in ad libitum fed rats maybe due to an overload phenomenon. That is the body can deal with food intakes up to a certain threshold, and that above this level the excess food accelerates aging.

A similar effect is seen with the development of age-associated proteinuria.[18] There are small increments in protein excretion as food intake rises from 12.5 to 25 to 50 kcal per day, but above this level the excess food has a major accelerating effect on proteinuria development.

Dietary Constituents

The effect of dietary composition was studied in a long term food restriction experiment.[18] The possible aging effects of high protein (casein) high fat (maize oil) and high carbohydrate (sucrose) diets were studied when fed at half the ad libitum energy intake. In the case of collagen aging there was no difference whether the diet was rich in fat, carbohydrate or protein, because the energy content regardless of source, determined the rate of aging.[12] However, the development of age-associated proteinuria was determined by both energy intake and protein intake[18] as shown earlier by Bras and Ross.[19] for the development of age associated renal disease.

Central Control of Aging

The studies just described have shown that pituitary and dietary factors can affect the rate of aging. It was also shown that temperature may determine the rate of aging in tendon collagen. Since there are areas in the hypothalamus which regulate pituitary function, feeding behaviour and body temperature, it is tempting to propose (Fig. 3) that the hypothalamus has

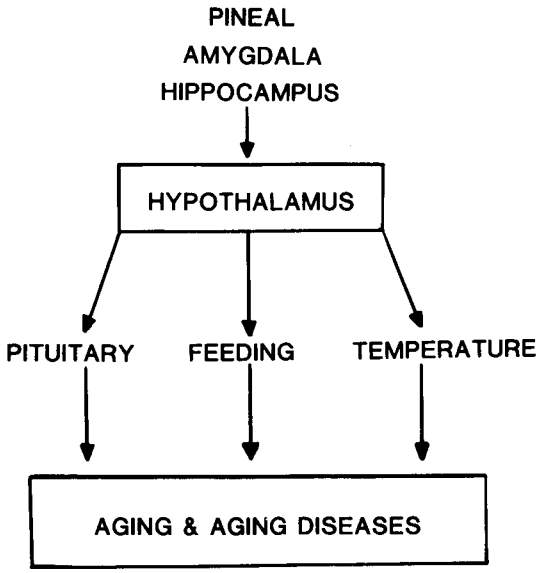

Fig. 3 The hypothalamic regulation of aging and the development of aging diseases by mediation of the pituitary, feeding and temperature.

one or more areas or clocks that time the rate of aging.[20] The hypothalamus is in turn influenced by higher centres such as the amygdala, hippocampus, pineal, etc. Thus there are probably a number of centres in the brain working together to time the rate of aging by modulating pituitary hormone secretion, food intake and temperature.[21]

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