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MINIREVIEW: Aging and Anti-Aging Effects of Hormones

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Hormones can promote or inhibit aging depending on the experimental conditions employed. The aging effects of hormones are demonstrated by reducing hormone secretion by hypophysectomy or chronic underfeeding in young or mature rats. These result in depressing whole body metabolism, growth, body temperature and blood glucose levels, heart rate and vital capacity, gene expression, etc., but delaying aging of tissues, suppressing development of pathology and tumors, and, in underfed rats, prolonging life span. The anti-aging effects of hormones are demonstrated by elevating hormone levels in old rats whose hormones have declined as a result of dysfunctions that develop in the neuroendocrine system with age. An increase of hormones in these rats promotes gene expression, elevates protein synthesis, and enhances metabolism, growth, and function of stimulated organs and tissues.

DO hormones accelerate or inhibit aging processes? One of us (AVE) provides evidence here that hormones can hasten aging developments, whereas the other (JM) shows that hormones can inhibit or reverse some aging processes. It will be seen that hormones can elicit both effects, but first it is necessary to define aging and clarify the criteria by which the actions of hormones on aging are determined. We define aging as a general decline in body functions with age, associated with a decrease in ability to maintain homeostasis. Hormones secreted by the neuroendocrine system (hypothalamus, pituitary, target glands, and tissues) are essential for normal development of body organs and tissues and for their functional maintenance throughout life. They also determine the rate of tissue metabolism and thereby participate in regulating aging of body tissues and life span.

Proof that hormones can accelerate aging changes is based mainly on long-term experiments in young or middle-aged rats or mice showing that hypophysectomy, ablation of other endocrine glands, or reduced caloric intake, all of which decrease secretion of hormones (Campbell et al., 1977), delay aging of many body tissues, inhibit pathology including tumor development, and prolong life, particularly in diet-restricted animals (Wyndham et al., 1987; Everitt, 1988; Masoro, 1988). The criteria used for assessing the anti-aging effects of hormones are based mainly on shorter term studies in old rats showing that (a) a general decline in secretion of many hormones occurs together with a decrease in function of the organs and tissues they regulate, and (b) correction of these hormone deficiencies by neuroendocrine intervention can delay or reverse many of these decrements of aging (Meites, 1982, 1988; Meites et al., 1987). We shall review the evidence for the aging and anti-aging effects of hormones, and consider the mechanisms by which their effects are achieved.

Evidence That Hormones Can Promote Aging Processes

Much of the evidence for the aging action of hormones comes from long-term studies of rodents subjected to hypophysectomy, thyroidectomy, adrenalectomy, ovariectomy, or orchidectomy. Because loss of hormones by surgical removal of these endocrine glands slows aging in many tissues, and except for adrenalectomy is reported in a number of studies to prolong life, such hormones must directly or indirectly affect the rates of physiological aging and development of age-related disease (Everitt, 1973 1976c). Long-term hormone replacement therapy in endocrinectomized rodents and chronic hormone treatment of intact animals generally confirm the aging effects of hormones. Reduced food intake results in a general reduction in hormone secretion (Campbell et al., 1977), inhibits aging of many body tissues, retards development of pathology, and prolongs life in rats, mice, and other species (Weindruch, 1985; Masoro, 1988).

Pituitary hormones. — Pituitary hormones exert major effects on body function and aging. Hypophysectomy, by eliminating pituitary hormones and greatly reducing the secretion of hormones from the thyroid, adrenal cortex, and gonads, markedly decreases the rate of aging in most tissues (Everitt, 1973, 1988). Removal of the pituitary gland from young rats causes large reductions in metabolic rate (Denckla, 1974), growth (Everitt et al., 1980), and cardiovascular functions (Beznak, 1963). As these functions are maintained at low levels throughout life, hypophysectomized rats might be expected to have a reduced rate of aging on the basis of the "wear and tear" theory of aging.

In humans, in contrast to rats, hypophysectomy and hypopituitarism have been reported to produce symptoms characteristic of aging (Everitt, 1966; Timeras, 1983). The best evidence for the anti-aging action of hypophysectomy comes from studies of tail tendon collagan aging in rats. Long-term hypophysectomy retards collagen fiber aging using both Verzar's classical thermal-contraction test (Verzar and Spichtin, 1966) and the urea time-to-break test (Olsen and Everitt, 1965). There is a large increase in collagen fiber tensile strength with age, and the rate of increase is halved by hypophysectomy and reduced by 30% in food-restricted rats when both groups consume the same quantity of food

(Everitt et al., 1983). Adrenocortical steroids can accelerate collagen aging (Everitt, 1973, 1981) and may be secreted in greater amounts in partially starved rats (Stewart et al., 1988). It is generally assumed that age changes in tail tendon collagen mirror collagen aging in other tissues. This was shown to be true for collagen aging in dorsal skin, which is also retarded by hypophysectomy (Verzar and Spichtin, 1966).

Kidney aging is likewise reduced markedly by hypophysectomy in the young rat, and the effect is greater than that of food restriction (Wyndham et al., 1987). Like collagen aging, the rate of thickening of glomerular basement membrane (GBM) with age is halved by hypophysectomy and reduced by about 30% in food-restricted rats (Wyndham et al., 1987). There is evidence that growth hormone may be the pituitary factor concerned in GBM thickening (Oikawa et al., 1985). Hypophysectomy also slows thickening of basement membranes in the kidney tubule (Everitt, 1976a) and gastrocnemius muscle (Everitt et al., 1985). Age-related renal enlargement, development of glomerulosclerosis, proteinaceous casts, and proteinuria were all markedly inhibited by hypophysectomy (Wyndham et al., 1987).

Age-related changes in gastrocnemius muscle of the hind limb of the rat, such as atrophy, structural and ultrastructural changes, and development of hind leg paralysis are all inhibited by hypophysectomy in the young rat and by food restriction begun at the same age (Everitt et al., 1985). Morphometric studies show that hypophysectomy is more effective than food restriction in reducing fiber atrophy in old gastrocnemius muscle (Shorey et al., 1988).

Gross pathology in old age is reduced in both hypophysectomized and food-restricted rats (Everitt et al., 1980). Comparative data reveal gross pathology at autopsy in 100% of male controls aged 800 days or more, but in only 74% of food-restricted and 48% of hypophysectomized rats (Everitt, 1988). Similarly, tumors were seen at autopsy in 67% of male controls, in 34% of food-restricted rats, and in only 12% of hypophysectomized rats (Everitt et al., 1980). This much lower incidence of pathology, particularly tumors, indicates that hormones of the pituitary and target glands play an important role in development of these diseases of old age. The hormonal role in tumorigenesis is well established (Furth, 1975). Prolactin is essential for mammary tumor development in rats and mice, and development of these as well as pituitary tumors in old female rats is associated with high prolactin secretion (Meites, 1982, 1988). In elderly men and women, there is no evidence for any significant change in prolactin secretion, and prolactin has not been demonstrated to be important in the development of breast cancer in women (Furth, 1975).

Retarded aging of immune functions in old hypophysectomized rats may account for some of the reduced pathology in these animals. Long-term hypophysectomy improves the rejection of xenografts (Bilder and Denckla, 1977), enhances the response to immunization with sheep erythrocytes (Scott et al., 1979), and delays thymic involution (Harrison et al., 1982) in older rodents.

The life duration of hypophysectomized rats housed under good conditions at 27°C (the thermoneutral temperature) is greater than that of intact controls even when no replacement therapy is given (Everitt, 1988). Early studies recorded short life durations after hypophysectomy (Smith, 1930; Everitt, 1966; Verzar and Spichtin, 1966), probably because of inadequate housing conditions. Long-term hypophysectomy reduces the incidence of many life-threatening diseases (Everitt, 1988), but by diminishing adrenocortical function it increases sensitivity to stress and by decreasing thyroid hormone secretion it impairs the long-term thermogenic response to cold, causing body temperature to fall. For the successful survival of hypophysectomized rats into old age they should be protected from stress and especially low temperature. Cortisone acetate injections were found to prolong the life of hypophysectomized rats (Everitt, 1976a; Everitt et al., 1980). When rats were hypophysectomized at 60 days by the transauricular technique and injected subcutaneously once weekly with 1 mg cortisone acetate, their mean life duration was 916 days compared with 858 days for food-restricted rats on the same food intake and 785 days for ad libitum-fed controls. In studies extending over a 25-year period, maximum life durations were 1201 days for ad libitum-fed controls, 1515 days for food-restricted rats, and 1352 days for hypophysectomized rats (Everitt and Wyndham, 1982). Hypophysectomy is not as good as food restriction for extending the life of the rat, because the optimum hormone replacement therapy has yet to be determined.

Hypophysectomy in adult rats with thyroid and corticosteroid maintenance was found by Denckla (1976) to restore youthful competence in immune functions (Scott et al., 1979), vascular responsiveness to beta adrenergic stimulation (Parker et al., 1978), hepatic RNA synthesis (Bolla and Denckla, 1979), and oxygen consumption (Denckla, 1974). Denckla (1974) postulated that aging results from the action of an unidentified Decreasing Oxygen Consumption Hormone (DECO) produced by the pituitary, which programs aging. However, this hypothetical hormone has not been isolated from the pituitary, and there is no evidence for the existence of a specific aging hormone.

Ovarian aging appears to be retarded by hypophysectomy at an early age in three strains of mice (Jones and Krohn, 1961). The rate of oocyte loss in aging mice is halved by hypophysectomy. Obviously, pituitary gonadotropins accelerate the loss of oocytes; however, a long-term study with gonadotropin replacement therapy is required to confirm this. It must be emphasized that not all age changes are affected by hypophysectomy. Two morphological age changes (testes-like tubes and epithelial cellular cords) develop in the ovary of the aging hypophysectomized rats and hence may be independent of pituitary hormone control (Crumeyrolle-Arias and Aschheim, 1981).

Adrenocortical aging is delayed in hypophysectomized rats. In old hypophysectomized rats the content of age pigment is greatly reduced (Walton et al., 1988), and age-related enlargement of the adrenal is absent (Everitt and Wyndham, 1982).

Thyroid hormones. — Thyroidectomy, like hypophysectomy, reduces metabolic rate, lowers food intake, decreases growth, and slows the rate of collagen fiber aging in rat tail tendon (Giles and Everitt, 1967; Everitt et al., 1969). Thyroidectomy also decreases GH, ACTH-glucocorticoid, and

gonadotropin secretion (Martin and Reichlin, 1987). Replacement therapy with thyroxine restores collagen aging to normal in ad libitum-fed rats but not in food-restricted rats (Giles and Everitt, 1967). This suggests that the aging action of thyroxine may be mediated by some food factor, e.g., glucose or a metabolite such as an oxygen-free radical. Very similar effects of thyroxine and food were seen in development of age-associated renal disease as monitored by proteinuria (Everitt, 1976b).

Thyroxine injections over a period of 5 months in old rats increased food intake from 22g to 32g per day, accelerated collagen fiber-breaking time from 185 to 250 minutes (Everitt et al., 1969), and increased development of renal disease (Everitt and Porter, 1976). Berg (1966) showed that continuous administration of thyroxine in drinking water increased the severity of nephrotic lesions in the kidney of aging rats. Thyroid hormones have been shown to have maturational effects on brain (Dussault and Ruel, 1987) and to increase bone age in hypophysectomized rats (Asling et al., 1954). Neonatal administration of thyroxine produces a state of hypothyroidism which, like hypopituitarism, leads to an extension of mean life duration (Ooka et al., 1983). Long-term administration of thyroxine in nontoxic doses shortened the life duration of Wistar rats (Ooka and Shinkai, 1986) and mice (Brailsford-Robertson, 1928).

Adrenocortical hormones. — Because the adrenal cortex is essential for life, complete adrenalectomy is rapidly fatal and leads to death of most rats within a week or so. However, 1% sodium chloride in drinking water prolongs life and, if given with a very low dose of cortisol in the drinking solution, permits survival into old age (Landfield et al., 1981). There is evidence that long-term adrenalectomy retards certain morphological age changes in the hippocampus (Landfield et al., 1981), and that prolonged glucocorticoid treatment accelerates these age changes (Landfield et al., 1980; Sapolsky et al., 1986). Glucocorticoid damage to the hippocampus involves loss of corticosterone receptors, astrocyte hypertrophy, and death of neurons.

The actions of adrenocortical steroids on aging processes in Cushing's syndrome were discussed by clinicians many years ago (Findley, 1949; Solez, 1952) and later demonstrated in stressed animals (Selye and Tuchweber, 1976), including repeatedly bred rats (Wexler, 1964) and spawning Pacific salmon (Robertson et al., 1961). Oversecretion of glucocorticoids increases cardiovascular age changes such as arteriosclerosis, hypertension, cardiac hypertrophy, and coronary heart disease in rats (Wexler, 1976; Bassett and Cairncross, 1977).

Glucocorticoids have immunosuppressive actions that may promote tumor growth in aging rats (Sapolsky and Donnelly, 1985) and mice (Walker et al., 1978). Long-term low cortisone therapy was found to increase tail tendon collagen aging in hypophysectomized rats (Everitt, 1973), while pharmacological doses of cortisol increased collagen aging in tail tendon of intact female rats (Arvay and Takacs, 1965).

Ovarian hormones. — The ovary secretes estrogens and progesterone during reproductive life, and the secretion of these hormones is controlled by hypothalamic GnRH, which promotes release of pituitary gonadotropins (LH and FSH). Long-term ovariectomy in rodents delays a number of age-associated changes in the hypothalamus, preventing loss of estrous cycles in rats with ovarian grafts (Aschheim, 1976), loss of gonadotropin surges (Mobbs et al., 1984), and increased glial activity in the arcuate nucleus (Schipper et al., 1981). A growing literature shows that estrogens secreted by the ovary promote these hypothalamic age changes (Finch and Landfield, 1985). Chronic administration of estrogen was found to damage neurons in the arcuate nucleus and medial basal hypothalamus (Brawer et al., 1978; Sarkar et al., 1982).

Estrogens promote, whereas ovariectomy inhibits, a number of other age-related processes in rodents. Ovariectomy at an early age slows the rate of collagen aging in rat tail tendon (Arvay, 1976), whereas estradiol administration increases the incidence of senile osteoarthrosis in mice (Silberberg and Silberberg, 1971). Mammary and pituitary tumors commonly seen in old rodents appear to be due to the decline in hypothalamic dopamine (DA) and to the action of estrogen, leading to increased prolactin secretion (Sarkar et al., 1983). Ovariectomy reduces the incidence of mammary tumors in old mice (Bittner, 1948). Long-term administration of estrogen to ovariectomized rodents promotes development of these tumors by reducing hypothalamic DA and increasing secretion of prolactin (Sarkar et al., 1983).

The widespread clinical use of estrogen to inhibit osteoporosis in postmenopausal women brings with it increased risk of endometrial carcinoma, cardiovascular problems, and gall bladder disease (Gambrell, 1982). The carcinogenic action of estrogen may be due to the release of free radicals from catechols formed during metabolism. There are a number of reports associating elevated plasma estrogen levels with increased risk of coronary heart disease in men (Chute et al., 1987).

Testicular hormones. — Despite the early pioneering work of Brown-Séquard (1889) with human rejuvenation experiments, present knowledge of the action of testicular hormones on aging is very meager. Testosterone is believed to have a life-shortening action in males as well as an aging action on a number of tissues (Hamilton, 1948). Castration is reported to increase the life duration of Pacific salmon (Wexler, 1976), lampreys (Larsen, 1985), rats (Asdell et al., 1967), and human inmates in a mental institute (Hamilton and Mestler, 1969). The prostate is a major target organ of testosterone. Cancer of the prostate, a major cause of death in elderly men, was not seen in eunuchs or eunuchoids (Moore, 1944). Similarly, benign prostatic hypertrophy occurs in most men in old age, but not in patients castrated prepubertally (Moore, 1947).

Testosterone acts on other tissues, promoting age changes in bone (Silberberg and Silberberg, 1971), and similarly in the kidney, where castration in young rats inhibits the development of age-related proteinuria up to 200 days (Sellers et al., 1950). Such proteinuria rises progressively throughout life (Wyndham et al., 1987). Wexler (1964) found that repeatedly bred male rats develop arteriosclerotic lesions at an earlier age than their unmated controls.

Adrenal catecholamines (CAs). — During periods of stress the adrenal medulla and sympathetic nerve endings secrete increasing quantities of epinephrine and norepinephrine (NE). These CAs even in small doses have been shown in animal studies to damage arteries, causing lipid deposition in the media (Lorenzen, 1963; Haft, 1974). Caruthers (1969) postulated that the stresses of modern living, by maintaining high levels of CAs, are capable of producing atheroma. This is more likely to occur in hard-driving, competitive individuals who are prime candidates for coronary heart disease (Friedman and Rosenman, 1974; Friedman et al., 1975; Rosenman et al., 1975). There is a large volume of clinical, epidemiological, and experimental evidence showing that repeated exposure to stress over long periods damages not only the cardiovascular system but also digestive, immune, nervous, and skeletal muscular systems (Levi, 1971; Gunderson and Rahe, 1974; Rabkin and Struening, 1976; Cooper, 1984; Gentry, 1984). However, tissue injury in stress may be caused by a number of nervous and hormonal factors, especially CAs and glucocorticoids that interact (Di Giusto et al., 1971; Bassett, 1983). Some of the damaging action of CAs may be due to the release of oxidative free radicals (Wise, 1984). The increased circulating levels of CAs in the elderly (Prinz et al., 1984) may contribute to tissue aging.

Evidence That Hormones Can Delay or Reverse Aging Processes

There is a reduction in secretion of many hormones with age in rats and humans. In the rat there is a decline in secretion of hypothalamic GnRH, GHRH, dopamine, norepinephrine, and vasopressin; in pituitary LH, FSH, TRH, and GH; and in gonadal hormones, thyroxine, somatomedins, insulin, and perhaps other hormones (Meites et al., 1987; Meites, 1988). Whether secretion of ACTH-adrenal cortical steroids and of TSH is altered in old rats is not clear at present. The decrease in TSH levels in old male rats does not appear to be significant (Simpkins et al., 1977), despite a decline in thyroxine secretion. Secretion of only one hypothalamic hormone appears to be increased with age in the rat, namely somatostatin (Sonntag and Meites, 1988). Prolactin secretion is elevated in old rats due to a decrease in hypothalamic DA (Meites et al., 1987; Meites, 1988). It has been claimed that ACTH secretion is increased (Tang and Phillips 1978; Landfield et al., 1980; Sapolsky et al., 1986), but this has been contradicted by others (Riegle, 1983). There is also a decrease in pituitary response in old rats to GnRH, GHRH, CRH, and TRH (Meites, 1988), in gonadal response to gonadotropins (Harman and Talbert, 1985), and in response of other tissues to hormones due to loss of receptors or to post-receptor cellular events (Roth, 1985). In elderly humans, there is a decline in secretion of gonadal hormones, GH, somatomedins, vasopressin, and perhaps other hormones, but there is an increase in secretion of gonadotropins due to the decrease in gonadal hormone secretion. The declines in hormone secretion with age are believed to contribute to many decreases in body functions in animals and man. The evidence that hormones can produce anti-aging effects comes mainly from studies in older rats that demonstrate that hormone elevation can inhibit or reverse certain aging changes.

Reproduction. — Estrous cycles become irregular in female rats at 7–8 months of age, and by 10–15 months they enter a constant estrous state and cease to cycle. Aging male rats show a decline in testosterone secretion and perhaps a decrease in spermatogenesis (Meites, 1988; Harman and Talbert, 1985), but healthy old males may continue to reproduce practically to the end of life. Although the pituitary of old rats becomes less responsive to GnRH stimulation (Meites et al., 1987; Meites, 1988) and the gonads to gonadotropic hormones (Harman and Talbert, 1985), neither pituitary nor gonads are mainly responsible for the reproductive decline in rats. When the ovaries of old noncycling rats were transplanted to young ovariectomized rats (Aschheim, 1976; Peng, 1983), or when the pituitary of old rats was transplanted to young hypophysectomized rats (Peng 1983), cycling resumed in many of these animals.

The major cause for the reproductive decline in rats is due to dysfunctions that develop in the hypothalamus (Meites, 1982, 1988). The most important of these is the decrease in CAs, particularly NE, which promotes GnRH release from the hypothalamus into the pituitary portal vessels. NE is reduced in the hypothalamus of old male and female rats (Simpkins et al., 1977; Meites, 1982), and this leads to decreased GnRH release from the hypothalamus (Wise and Ratner, 1980; Meites, 1988).

Administration of L-dopa, which increases brain CAs, delays loss of estrous cycles and induces resumption of cycles in aging constant estrous rats (Meites, 1982; Meites et al., 1987). Administration of other central-acting drugs that increase hypothalamic CAs can also reinitiate estrous cycles in old constant estrous rats. Estrous cycles were induced in old pseudopregnant rats by administration of a dopaminergic ergot drug, which reduces the high PRL secretion characteristic of pseudopregnant rats (Clemens and Bennett, 1977). Direct electrical stimulation of the hypothalamus can also induce ovulation in old constant estrous rats, presumably by inducing GnRH release (Clemens et al., 1969). Other neurotransmitters in addition to the CAs may be involved in the reproductive decline in rats, but little is yet known of their role (Simpkins et al., 1977). The decrease in hypothalamic CAs in old rats appears to be due to loss or damage of catecholaminergic neurons as a result of the chronic action of several hormones, particularly estrogens (Brawer et al., 1978; Sarkar et al., 1982, 1984), to free radicals from oxidation of hypothalamic CAs, a decrease in tyrosine hydroxylase (the rate-limiting enzyme for synthesis of CAs), an increase in monoamine oxidase (catabolizes CAs), the presence of possible toxic agents, metabolic "wear and tear" from prolonged usage, and other possible causes (Meites et al., 1987; Meites, 1988).

Cessation of menstrual cycles in women and the decline in testosterone secretion in aging men are also caused by hormone deficiencies, but unlike rats, the primary fault appears in the gonads rather than in the hypothalamus. Beginning a few years prior to the menopause, the ovaries exhibit a progressive decline in ability to secrete estrogen and progesterone, resulting in an elevation in secretion of

gonadotropic hormones. In the postmenopausal period, the ovaries atrophy and lose their follicles and ova, and a further elevation occurs in secretion of gonadotropic hormones. In aging men, there is decreased secretion of testosterone by the testes, which also results in a rise in gonadotropins, although these do not reach the high levels seen in postmenopausal women (Harman and Talbert, 1985).

GH secretion and protein synthesis. — GH is the most important protein anabolic agent in the body, and is essential for protein synthesis throughout life. GH has been shown to be important for body growth, including growth of bone, and for normal kidney, liver, pancreatic, immune, and other functions. It is well established that there is an age-related decline in protein synthesis and turnover in both animals and humans (Richardson, 1981), who stated that the decline in protein turnover provides the molecular basis for many physiological changes associated with senescence.

GH secretion in old male (Sonntag et al., 1980; Sonntag and Meites, 1988) and female rats (Takahashi et al., 1987) declines, and there is also a decrease in somatomedin secretion (Florini and Roberts, 1980; Takahashi and Meites, 1987), which is normally promoted by GH action. A significant reduction in GH and somatomedin secretion has also been demonstrated in elderly human subjects (Florini et al., 1985).

GH secretion is directly controlled by two hypothalamic peptide hormones, GHRH, which promotes GH secretion, and somatostatin, which inhibits GH secretion. There is evidence that GHRH content in the hypothalamus of old rats is reduced (Morimoto et al., 1988), and that release of somatostatin is increased (Sonntag and Meites, 1988). Both DA and NE, but particularly NE, can elevate GH secretion in animals and man (Martin and Reichlin, 1987), presumably by promoting GHRH release and perhaps also by reducing somatostatin release (Sonntag and Meites, 1988). DA and NE are significantly decreased in the hypothalamus of old rats (Meites et al., 1987; Meites, 1988), and there is evidence that these are also decreased in the hypothalamus and other brain areas of elderly man (Hornykiewicz, 1986).

Injection of L-dopa into old male rats for 8 days raised circulating GH levels to the same values as those in young male rats, and partially elevated protein synthesis in the old rats as measured by incorporation of tritium-labeled phenylalanine into protein (Sonntag and Meites, 1988). Administration of bovine GH for 8 days returned protein synthesis in diaphragm muscle of old male rats to the same level as in young male rats. Injection of GH for 10 days into old female rats significantly increased the weight of liver, kidneys, heart, and spleen, and also elevated thymus weight in old mice (Sonntag and Meites, 1988). Kelley et al. (1986) reported that GH administration in old rats restored thymic function, as measured by five function tests, to the same level as in young rats. The thymus is considered to be the chief component of the immune system.

It is clear that in the aging rat, the reduction in hypothalamic DA and NE is mainly responsible for the decrease in GH (and somatomedin) secretion, and probably accounts to a large extent for the reduction in protein synthesis, immune function, and perhaps other body decrements. It may also account for the decrease in GH and somatomedin secretion in elderly human subjects.

Gonadal hormones. — Gonadal hormones are generally associated with youth and vigor, and are responsible for development of the reproductive tract, mammary glands, female sex characteristics, etc. The marked decline in secretion of gonadal hormones with age is believed to account at least in part for the decrease in physical and mental vigor, the reduction in sexual activity, and loss of bone. Estrogen or estrogen in combination with a progestin are considered to be appropriate treatments for prevention of osteoporosis in postmenopausal women (Gosden, 1985), even though the risk of endometrial cancer may be increased.

Androgens are not widely employed in treating elderly men, but in old men with severe hypogonadism they may increase sexual potency, muscular strength, and provide a sense of well being (Morley, 1988). The danger is that they may also produce enlargement of the prostate, water retention, polycythemia, hyperlipidemia, and liver dysfunction (Morley, 1988).

Adrenal hormones. — There is no clear agreement that basal secretion of glucocorticoid hormones is altered with age (Riegle, 1983), although increased corticosterone levels have been reported in old rats under some conditions (Landfield et al., 1978). Treatment with glucocorticoid hormones was reported to prolong life in hypophysectomized rats (Everitt et al., 1980; Everitt, 1988), in a short-lived strain of mice (Bellamy 1968), and in the NZB/NZW mouse strain subject to autoimmune disease (Walker et al., 1978). The life span of human diploid cells when cultured in vitro was significantly increased by incorporation of glucocorticoids in the culture medium (Cristofalo and Kabakjian, 1975).

Dehydroepiandrosterone (DHEA), an adrenal cortical steroid, was reported to decrease significantly with age in man (Orentreich et al., 1984), but not in mice (Cutler et al., 1978). It was observed to inhibit several age-related pathological manifestations, including tumor development. It was also shown to have anti-obesity and anti-diabetic qualities (Schwarz, 1985; Regelson et al., 1988).

Discussion

It is clear from the evidence cited here that hormones can produce aging or anti-aging effects, depending on the experimental conditions employed. Hypophysectomy, other endocrine ablations, or caloric restriction, acting over long periods of time in young or mature animals, can preserve the morphological and functional integrity of tissues, inhibit development of pathology and tumors, and lengthen life span, especially in calorie-restricted rats (Everitt, 1988; Masoro, 1988). On the other hand, elevation of initially low levels of hormones in old rats can induce resumption of estrous cycles, increase testosterone secretion in old male rats, elevate GH and somatomedin secretion, promote protein synthesis, and restore thymus size and function (Meites et al., 1987; Meites, 1988; Kelley et al., 1986). An increase in hypothalamic dopamine also induces regression of mammary and pituitary tumors. Estrogens or estrogen-progestin combinations can inhibit bone loss in postmenopausal

women (Gosden, 1985), and adrenal glucocorticoid hormones administration can prolong life span of hypophysectomized rats (Everitt, 1988), and promote doubling of fibroblast cells in culture (Cristofalo and Kabakjian, 1975).

The favorable effects of hypophysectomy or of dietary restriction (usually reduced by 40 or 50%) on aging are believed to be produced by eliminating or reducing hormone secretion (Meites, 1989). However, neither hypo- nor hypersecretion of hormones can be considered to be desirable, since both can produce deleterious effects, as amply illustrated in the clinical literature. Some of the undesirable effects of a chronic elevation of hormone levels have been reviewed here. A chronic reduction in hormone levels by hypophysectomy or underfeeding leads to inhibition of body growth and development in young rats, loss of body weight in mature rats, lower ability to maintain normal body temperature and blood glucose levels, decreased resistance to stress, less capacity to perform muscular work, lower vital capacity, etc. These effects are more pronounced in hypophysectomized than in food-restricted rats unless hormones are replaced. Paradoxically, many of these effects of hypophysectomy or of food restriction resemble some of the symptoms observed in old animals and man. It has been noted that many of the changes observed in hypopituitary human subjects are similar to those of aging individuals (Everitt, 1966; Timeras, 1983). Therefore, the anti-aging effects of hypophysectomy or of dietary restriction are achieved at the expense of a lengthy reduction in homeostasis and normal body functions.

The mechanisms by which hormones exert their aging or anti-aging effects are not entirely clear. Since hormones are essential for normal body operations, their effects on aging processes cannot be separated from their normal actions. Hypophysectomy and food restriction, by reducing hormone levels and perhaps also by decreasing availability of nutrients to tissues, decrease the work (metabolism) of these tissues, thereby slowing their morphological and functional decline. Although food restriction was reported not to reduce the metabolic rate per unit of lean body mass (Masoro, 1988), the total body metabolism is decreased as compared to that of ad libitum-fed controls. Hypophysectomy has also been shown to result in a reduction in body metabolism (Denckla, 1974). The decrease in hormones also is believed to reduce gene expression in tissues and perhaps decrease free radical damage. Since "wear and tear" on organs and tissues by chronic usage is depressed during underfeeding, this preserves and extends their lifetime functional capacity, thereby inhibiting development of defects (pathology) and prolonging life span.

The anti-aging effects of hormones have been demonstrated mainly in old rats. In these animals there is a decrease in secretion of most hormones and in the body functions they control. Elevation of hormone levels in these rats inhibits or reverses a number of well-recognized aging changes. The reproductive decline is reversed, protein synthesis is increased, and thymic function is improved (Kelley et al., 1986; Meites, 1988; Meites et al., 1987). It is possible that chronic elevations of hormone levels in old rats, while improving certain body functions, may shorten their life span. Prolonged elevation of hormones in old rats has not yet been tested. Ooka and Shinkai (1986) reported that chronic hyperthyroidism instituted early in life reduced the life span of rats, but the dose of thyroxine administered may have been in the pharmacological rather than in the physiological range. Ideally, the doses of hormones given to old rats should be sufficient only to return hormone levels to those present in young or mature rats. In a study in a short-lived strain of mice, Cotzias et al. (1974) reported that L-dopa administration increased their life span. Further research is warranted to resolve this question. Inasmuch as old rats already show a reduction in hormone secretion and body functions as compared to these in young rats, it is doubtful that a further decrease in hormone secretion and body functions by underfeeding would inhibit aging processes. On the contrary, an elevation of hormone levels is needed to inhibit aging and return body functions to youthful levels.

In conclusion, the aging effects of hormones are demonstrated in young or mature animals by reducing hormone secretion, thereby decreasing gene expression and metabolism, and delaying aging of organs and tissues. The anti-aging effects of hormones are demonstrated by elevating the low levels of hormones secreted by old rats, thereby promoting gene expression, elevating protein synthesis, and stimulating growth and function of depressed organs and tissues.

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