Obesity in middle-aged humans is a risk factor for many age-related diseases and decreases life expectancy by about 7 years, which is roughly comparable to the combined effect of all cardiovascular disease and cancer on life span. The prevalence of obesity increases up until late middle age and decreases thereafter. Mechanisms that lead to increased obesity with age are not yet well understood, but current evidence implicates impairments in hypothalamic function, especially impairments in the ability of hypothalamic pro-opiomelanocortin neurons to sense nutritional signals. The rapid increase in the prevalence of obesity at all ages in the past decade suggests that, in the next two or three decades, diseases associated with obesity, especially diabetes, will begin to rise rapidly. Indeed, these trends suggest that for the first time in modern history, the life expectancy of people in developed societies will begin to decrease, unless the rapid increase in the prevalence of obesity can be reversed.

Introduction

The relation between obesity and aging is of great concern for several reasons. First, obesity decreases life span (1) and, conversely, caloric restriction increases life span (2). Furthermore, obesity is a risk factor for age-correlated diseases (3-6). Finally, the prevalence of obesity increases with age but, most alarmingly, in the past decade the prevalence of obesity in the United States has increased dramatically in all age groups (Fig. 1). Despite the compelling relation between obesity and aging, however, little is known about why obesity increases with age or why obesity is a risk factor for age-related diseases. However, as described herein, it is clear that the relation between obesity and aging is complex.

Morbidity and Mortality

Obesity is associated with increased disease and mortality . . . to a point

Obesity is of particular interest because it is a major risk factor for disease and mortality (the likelihood of dying). In general, the prevalence of most age-related diseases, including diabetes, cardiovascular disease, and cancer, increases with increasing body mass index (BMI) (5, 7-10). Body weight varies with both adiposity (amount of fat) and height. The amount of body fat is the main risk factor for disease; thus, obesity is quantified using BMI, which is calculated as weight in kilograms divided by the square of height in meters. “Overweight” is defined as a BMI between 25 and 25.9, and “obesity” is defined as a BMI of over 30. In one study, the adjusted prevalence ratio of diabetes (roughly, the fold increase in the risk of developing diabetes in overweight people as compared with individuals of normal weight) increased from 3.2 in overweight men under 55 years of age to 18.1 in the most obese class of men (8). Similar results were obtained in women under the age of 55. In other words, the most obese men (under 55) were nearly 20 times as likely to be diabetic as were normal-weight individuals. However, as with hypertension, the concerns about diabetes stem not so much from the disease itself as from the fact that diabetes is a risk factor for complications such as cardiovascular disease. In this respect, it is of some interest that, although obesity is a risk factor for cardiovascular disease, obesity only increases the likelihood of developing cardiovascular disease by about twofold, whereas obesity increases the likelihood of diabetes by nearly 20-fold in men under 55 years of age. Furthermore, the risk for diabetes that is associated with obesity decreases quite dramatically with age: In men over the age of 55, obesity increased the risk for diabetes only about threefold; similar results were obtained in women. These data suggest that obesity is much more dangerous under the age of 55 than it is over the age of 55.

In addition to being a risk factor for disease, obesity also reduces life span. Two recent studies similarly observed that obesity (BMI > 30) at age 40 reduced life expectancy by 6 to 7 years (11, 12). This effect of obesity on life span is particularly striking, because the complete elimination of cardiovascular disease and cancer combined would only increase life span by about 7 years (13). Thus, eliminating obesity would be expected to have about the same effect on life span as complete elimination of both cardiovascular disease and cancer. This conclusion is particularly compelling because, as described above, obesity is a major risk factor for both cancer and cardiovascular disease. Even being overweight (BMI between 26 and 29.9) between the ages of 45 to 54 years increased the lifetime risk of developing diabetes, hypertension, and coronary heart disease by threefold, twofold, and 50%, respectively (5), and decreased life expectancy by about a year (5) (see “Greasing Aging’s Downward Slide” http://sageke.sciencemag.org/cgi/content/full/2003/41/ns6). The observed effect of obesity on life span would be even greater than it is except that, although BMI during middle age is a risk factor for a variety of age-related diseases in later life (14) (see “All Fat Is Not Created Equal” http://sageke.sciencemag.org/cgi/content/abstract/2002/41/nw143), the effect of obesity on mortality rate decreases with age (15, 16).

Although diseases and mortality generally increase with increasing body weight, mortality risks also increase at very low body weight, following a classic “J-shaped” function. This latter association may reflect the effects of smoking (which decreases body weight and increases mortality) and disease. Thus, these two factors should be considered in epidemiological examinations of the relation between body weight and mortality. Nevertheless, a study that involved over 1 million Americans convincingly demonstrated that, between the ages of 30 and 74, the relative risk of a high BMI for mortality was higher in adults aged
30 to 44 than in adults aged 65 to 74, although even in the older group the risk was significant (17). Other evidence suggests that after late middle age, low body weight is a greater risk factor for mortality than is high body weight (18). However, this relation may reflect the fact that many diseases (especially cancer, an age-related disease) cause a reduction in body weight, and these diseases are more prominent in the elderly. Therefore, the association between low body weight and mortality probably reflects an effect of disease on body weight, rather than an effect of body weight alone on mortality (18). Although the precise role of disease in this instance remains to be determined, the relative importance of low body weight as a risk factor after late middle age probably reflects a relative reduction in the strength of the relation between body weight and mortality in the elderly (15). Thus, at a minimum, the relation between weight loss and mortality in the elderly is more complex than it is before late middle age: Weight loss is a better predictor of mortality than weight gain in the elderly, although the extent to which weight loss is a result of underlying disease is difficult to determine (18, 19). Therefore, in contrast to the clearly healthy effects of weight loss up until late middle age, the health effects of weight loss (especially by dieting) after late middle age are not as clear, although increased cardiovascular fitness through exercise (http://sageke.sciencemag.org/cgi/content/abstract/2002/2/nw7) is almost certainly valuable even at the oldest ages (16, 20).

Although much less information is available about the effects of obesity on life span in animal models, recent studies have suggested that, at least for diet-induced obesity (probably the best animal model for human obesity), the effect of obesity on life span appears to be similar in rodents and humans. In one study, obesity produced by an ad lib high-fat diet reduced life span in mice by 26% (21), and in another study a somewhat different high-fat diet reduced life span by 7% (22). It is of interest that these relatively modest effects of obesity on life span (7 to 26%) are much less than the opposite effect of caloric restriction, which can increase life span in rodents by 100% or more (2). This observation has mechanistic implications, because in the range of adiposity produced by caloric restriction (low normal), human data suggest a relatively modest effect of adiposity on life span. This is because a very low BMI is also a risk factor for mortality, and adiposity may even be protective at a low BMI. These observations suggest that the effects of caloric restriction are probably not mediated simply by a reduction of adiposity even through the same mechanisms by which adiposity decreases life span.

In considering the effects of obesity on disease and mortality, it should be noted that, in humans, the distribution of adipose tissue is probably more important in determining health outcome than is the total amount of adipose tissue or BMI. Many studies have demonstrated that waist-to-hip ratio is a much better predictor for both disease and mortality than is a simple BMI (23, 24). Although much less is known about the effect of waist-to-hip ratio on disease and mortality during aging, most general conclusions about obesity and aging appear to hold for waist-to-hip ratio and aging (25).

### The Obesity-Age Connection

**Obesity increases with age... to a point**

Not only does obesity increase disease and mortality, but the prevalence of obesity (that is, the proportion of obese individuals within a given population) itself increases robustly with age from puberty until late middle age [Fig. 1; data (http://www.cdc.gov/nccdphp/dnpa/obesity/trend/prev_char.htm) are derived from the Centers for Disease Control (http://www.cdc.gov)]. In 2001, 25.6% of Americans aged 60 to 69 years were obese, compared to only 14% of Americans aged 18 to 29. Although the prevalence of obesity decreases somewhat after age 70 (to 17%), it was still greater even at this advanced age than in young adults; indeed, the same trends were observed in studies conducted in each year represented in the chart. Even more alarming, however, the prevalence of obesity in all age groups, including the oldest, increased by at least 50% from 1991 to 2001 (Fig. 1). The age-related increase in the prevalence of obesity is reflected by the age-related increase in adiposity (amount of fat) observed in most human populations at least until 60 years of age; although adiposity declines thereafter, average adiposity remains higher than in young adults even into late senescence (16, 26-29). The age-related increase in adiposity is greater than the age-related increase in body weight or even BMI, because aging is associated not only with increased fat mass but also with monotonic decrease in muscles mass (30). Similar age-related increases in adiposity occur in most mammalian species, including nonhuman primates (31, 32), cats (33), dogs (34), rats (35), and mice (36, 37).

Although the prevalence of obesity clearly increases with age,

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**Fig. 1.** The percentage of obesity in an age-specific population (shown for each year and age range in years) increases with age and has grown over the past decade (source: Centers for Disease Control, Atlanta, GA).

It is important to note that body weight (and adiposity) increase asymptotically with age, reaching a maximum at around late middle age in humans and other species. Therefore, the incidence of obesity (that is, the rate at which new cases appear in the population) decreases with age. More precisely, the first derivative of obesity with respect to time is positive up until late middle age, after which it becomes negative; and the second derivative always decreases with age. Thus, as illustrated in Fig. 1, in 2002 the prevalence of obesity from the third to the fourth decade increased from 14 to 20.5% (an increase of 42%). From the forth to the fifth decade, the prevalence of obesity increased from 20.5 to 24.7% (an increase of 20.5%, almost exactly half the rate of new cases observed in the previous decade). Between the fifth and sixth decade, the rate at which obesity increases again declines by about half, and after the sixth decade, the prevalence of obesity actually...
These data are consistent with detailed studies conducted in rodents. For example, in C57Bl/6J mice, body weight increases (mainly as a result of an increase in fat mass) about 25% between 2 and 6 months of age, and increases an additional 25% between 6 and 18 months (at which age the body weight is close to maximum, although, on average, mice live until about 24 months of age). Thus the rate of increase in body weight is about three times faster between 2 and 6 months of age than it is between 6 and 18 months of age. To assess the development of insulin resistance (http://sageke.sciencemag.org/cgi/content/abstract/2002/21/nw73) with age in mice, we used hyperinsulinemic euglycemic glucose clamps, in which insulin sensitivity is reflected by the rate at which glucose must be infused to maintain constant blood glucose levels. Using this technique, we observed that insulin sensitivity decreases by about 50% between 2 and 6 months of age, but no significant changes in insulin sensitivity occur between 6 and 18 months of age (38). Similar results have been observed in rats, which (i) also exhibit a relatively rapid increase in body weight until middle age (between 2 and 12 months of age) followed by a decline after late middle age (between 24 and 31 months of age) (39), and (ii) show a large age-related decrease in insulin sensitivity between very young ages and middle age (between 2 and 9 months), but show a much smaller decrease in insulin sensitivity between 12 and 18 months (40).

Taken together, these data, which were obtained with a variety of organisms, demonstrate that although the prevalence of obesity (the proportion of the population that is obese) increases with age (that is, the derivative of prevalence with respect to time is positive until late middle age), the incidence of obesity (the second derivative of prevalence with respect to time) decreases with age. This slowing of incidence is in contrast to that observed for mortality and most age-related diseases, whose incidence rate increases (sometimes exponentially) with age (41, 42) (up to a point, after which the rate of change may decline). Thus, even though the incidence of obesity actually declines with age, the incidence of obesity-related diseases such as diabetes and cardiovascular disease, and of course, death, increases with age (up to a point). These observations raise the question of whether obesity should be considered a disease of the middle-aged (or even in some sense a developmental disease) rather than an age-, or to be more precise, senescence-related disease. As discussed above, this question is not merely semantic, because the relation between body weight and mortality also decreases monotonically with age, possibly disappearing altogether after 75 years of age (15). It could be argued that the reduction in the prevalence of obesity after late middle age could result from a selection effect. By this hypothesis, individuals susceptible to obesity (or susceptible to mortality caused by obesity) die before late middle age, leaving the elderly population to consist largely of obesity-resistant individuals. Although this hypothesis cannot be completely ruled out, the fact that the incidence rate of obesity decreases monotonically beginning in the third decade of life suggests that the reduction in the prevalence of obesity after late middle age is simply a continuation of a constant process that begins shortly after puberty.

Why Does Obesity Increase with Age?

Regardless of whether obesity is a disease of senescence or a post-maturational disease of middle age, the age-related increase in obesity certainly predisposes individuals to diseases and reduces life expectancy. Therefore, the largely uncharacterized mechanisms that mediate the age-related increase in obesity are of great biomedical significance. One plausible mechanism that may mediate the age-related increase in adiposity would be simple passive accumulation of adipose tissue over time. For example, if a few more calories are consumed than are expended each day over a long period of time, increased adiposity would result, as summarized by the pithy statement “A minute on the lips, forever on the hips.” Indeed, it has been argued that mechanisms that regulate body weight are inherently biased toward a slow accumulation of adiposity (43). However, such a mechanism would seem to imply a linear increase in adiposity with age, whereas adiposity increases asymptotically, with the incidence rate actually decreasing with age. Furthermore, such a mechanism would imply that eliminating excess adiposity through caloric restriction (“dieting” in the common parlance) would effectively reset the clock. If 20 pounds of fat accumulated between 30 and 50 years of age, then, after dieting to remove the excess 20 pounds, it should take another 20 years (or longer) to again accumulate 20 extra pounds. However, throughout most of the life span, this is not the case: Weight loss is usually only maintained for a relatively short period of time after dieting (44-46), attesting to the robust mechanisms that maintain relatively constant body weight (47). Similarly, in aging rodents, the age-related increase in body weight is robustly defended until well into late middle age. For example, subjecting female rats aged 4 and 16 months to caloric restriction for 10 weeks led to similar decreases in body weight in animals from both groups. Upon resuming ad lib feeding, the previously restricted rats from both age groups regained all the body weight lost, matching the body weights of the ad lib-fed controls by 3 weeks after resuming ad lib consumption (48).

Using a similar experimental design, we observed that 6-month-old rats regained all of the weight lost during 2 months of caloric restriction within 2 weeks after ad lib access to food was restored. Older (18-month-old) rats regained most, but not quite all, of the weight lost under the same conditions. These findings suggest that although body weight is actively defended during aging, this defense is somewhat less robust by late middle age than it is in young adulthood. On the other hand, we have observed that, in response to a 48-hour fast, 24-month-old male mice defend body weight just as robustly as 6-month-old mice; after refeeding, body weight increased as quickly in 24-month-old as it did in 6-month-old mice. The disparities in the results of these two series of experiments may result from species differences—old rats are much more obese than old mice—or from differences in the experimental protocols [caloric restriction (rats) versus complete fasting (mice)]. Also, fasting decreased the metabolic rate at least as robustly in 24-month-old as in 6-month-old mice. These latter observations argue against a simple passive accumulation of adiposity during aging and, instead, suggest that the age-related increase in adiposity is actively defended after weight loss well into late middle age. As observed in our studies in relatively old male rats, the defense of elevated adiposity also becomes impaired in elderly humans over the age of 65 (27-29). It is plausible that the loss of adiposity that occurs after late middle age results from (or at least is mechanistically related to) the impaired defense of body weight that also occurs after late middle age, but this hypothesis has not yet been directly addressed.

Body weight is also defended after overconsumption, so that after overconsumption-induced weight gain, homeostatic mechanisms are activated that cause a reduction in the original body weight before the overconsumption occurred. Just as people over...
the age of 65 exhibit attenuated responses to body weight reduction, they also exhibit an attenuated response to body weight gain (29). We have similarly observed that 24-month-old mice (well past late middle age) are more susceptible to diet-induced obesity than are younger mice. Specifically, 24-month-old mice gain weight more rapidly on an obesity-inducing high-fat diet than do 6-month-old mice (young adult). The age-related sensitivity to high-fat diets does not result from differences in caloric consumption but apparently results from differences in diet-induced metabolic rate. A high-fat diet increases metabolic rate (an apparent homeostatic response to defend body weight), and this activation is reduced in 24-month-old versus 6-month-old mice, even though on a regular chow diet the metabolic rates of mice from both groups are equivalent. In sum, obesity appears to increase with age because of an as-yet-undefined active mechanism, not a passive accumulation of fat. Although body weight may not be robustly defended at advanced ages, by then, adiposity has accumulated to such an extent that it remains elevated when compared to adiposity in young adults. Thus, two separate questions must be addressed: (i) Why is the age-related increase in adiposity defended through late middle age? (ii) Why is the defense of adiposity impaired toward the end of life?

On the whole, available data suggest that the hypothalamic “set point” for adiposity changes with age, so that incrementally higher body weights are defended at least through late middle age. Why is the higher adiposity defended? Recent studies have focused on the possible role of the protein leptin (http://sageke.sciencemag.org/cgi/content/full/2004/24/re4). Leptin is a hormone secreted from adipose tissue that can reduce body weight (Fig. 2); the absence of leptin has been shown to be one cause of massive obesity (49). One might hypothesize that age-related obesity results from a decrease in serum leptin concentrations with age. However, experiments have shown that up until late middle age, leptin production generally increases with age (50, 51) in humans (52) and rodents (37, 53) and is highly correlated with the observed age-related increase in adiposity. Just as adiposity declines after late middle age, so does leptin production. For example, in a geriatric population between the ages of 65 and 101, we have observed that serum leptin concentrations decrease linearly with age (51), and this reduction correlates with a reduction in BMI. Because a decrease in serum leptin concentrations leads to neuroendocrine responses, including an elevation in serum glucocorticoid concentrations (49), we examined the relation between leptin and plasma cortisol in this group of patients. In a multivariate analysis, cortisol concentrations correlated positively with age and negatively with leptin concentrations. We next sought to determine whether leptin and cortisol have a correlation that is independent of the age effect. After the effects of age were statistically adjusted for, cortisol concentrations continued to correlate with leptin concentrations; however, after the effects of leptin concentrations were statistically adjusted for, cortisol no longer correlated (that is, shared significant variance) with leptin concentrations. One interpretation of these data is that, in the geriatric population, the age-related increase in cortisol concentrations may result from an age-related decrease in plasma leptin concentrations, secondary to the loss of adipose mass in this elderly population.

Because leptin production increases with age up until late middle age, another plausible mechanism that might mediate the age-related increase in obesity would be that adiposity increases with age because of impairments in leptin signaling mechanisms. For example, as adiposity increases incrementally with age, plasma leptin concentrations also increase, which might cause a gradual desensitization of the leptin signaling pathways in hypothalamic neurons (Fig. 2A). A similar hypothesis has been proposed to explain the age-related decrease in insulin sensitivity (54). The desensitization hypothesis is appealing because leptin is a major signal that conveys to the hypothalamus the extent of adipose stores (49). Thus, a higher concentration of plasma leptin would be required to convey to the hypothalamus that a given amount of adiposity is present. Conversely, according to this hypothesis, in aging individuals, a reduction in plasma leptin concentrations after caloric restriction, even if youthful levels of plasma leptin were maintained, might trigger neuroendocrine mechanisms to restore body weight. This is because leptin insensitivity would prevent the current leptin concentrations from conveying an accurate indication of total adiposity. Consistent with findings that show that serum leptin concentrations increase with age, growing older is reported be associated with a decrease in the effectiveness of leptin to reduce food intake and body weight in rats (39, 55, 56) and mice (57). Furthermore, age-related leptin resistance was observed in old rats even after caloric restriction had produced 20-month-old rats with the same amount of body fat found in 3-month-old rats (58). These data suggest that age-related leptin resistance is not caused by increased adiposity, but instead that age-related obesity might be caused by the impaired effectiveness of leptin to reduce body weight. However, studies with leptin gene transfer suggest that although the leptin signaling system (Fig. 2B) may be attenuated in older leptin-resistant rats, impairments downstream of the leptin receptor may be more important in causing leptin resistance, as indicated by the induction of the signal transducer and activator of transcription-3 protein (STAT3) (Fig. 2B) (59). In these elegant studies, the leptin gene was transferred into the hypothalamus of 3- and 20-month-old rats, and responses to leptin, including food intake and body weight as well as leptin signaling (as reflected by STAT3 phosphorylation), were assessed at 9 and 26 days after gene transfer. Attenuation of leptin signaling was indicated by reduced STAT3 phosphorylation at 9 and 46 days after gene transfer in the old versus the young rats. However, the age-related impairments in physiological responses to leptin were much greater at 46 than at 9 days, even though the degree of STAT3 phosphorylation was similar at those time points. Furthermore, overproduction of leptin in transgenic mice does not prevent age-related increases in adiposity (60).

These key observations suggest the importance of determining the precise nature of the down-stream impairments in the development of age-related obesity. Among the most prominent downstream targets of leptin are nutrition-sensitive hypothalamic neuuropeptides (49). In particular, leptin stimulates the expression of hypothalamic pro-opiomelanocortin (POMC) (61), and leptin expression is elevated in mice that are obese as a result of impairments in the POMC product α-melanocyte stimulating hormone (α-MSH) (62). Conversely, expression of hypothalamic POMC is reduced in (obese) mice that do not express functional leptin or are insensitive to leptin (61). Furthermore, mutations in the POMC gene cause obesity (and consequent elevation of leptin) in humans (63, 64) and mice (65). Strikingly, many of the metabolic defects caused by leptin insufficiency are reversed by transgenic elevation of POMC throughout the mouse nervous system (66). These data suggest that many metabolic effects of leptin might be mediated by hypothalamic POMC. It is therefore of particular interest that hypothalamic POMC decreases with age in rats (67, 68), mice (69), and humans (70). These data suggest that
an age-related decrease in hypothalamic POMC gene expression may contribute to age-related increases in adiposity. It is not known why POMC expression decreases with age. One might expect that the increase in plasma leptin with age would lead to an increase in hypothalamic POMC gene expression.

POMC is a more likely candidate cause of the age-related increase in adiposity than are other leptin-regulated gene products, because some of these products do not change with age, and others show age-related changes in a direction that suggests a response to obesity rather than a cause (similar to the case with leptin). For example, in rats, expression of neuropeptide Y—a peptide neurotransmitter that stimulates feeding behavior—either does not change with age (53) or decreases with age (71). However, neuropeptide Y expression is elevated in mice that are resistant to leptin (61), and this elevated expression appears to contribute to the obesity of leptin-deficient mice (72). Therefore, neither impairment in the regulation of hypothalamic neuropeptide Y, nor a general hypothalamic resistance to leptin, appears to cause age-related obesity.

What accounts for the age-related decrease in hypothalamic POMC mRNA? Careful stereological analysis of POMC-producing neurons in mice indicates that the number of these neurons does not decline with age (73) (between 9 to 12 and 24 months of age, during which time adiposity increases by about 50%). However, in the leptin gene transfer study described above (59), the leptin transgene increased hypothalamic POMC gene expression in young, but not old, rats. Furthermore, we have observed that feeding-induced activation of the POMC neurons, as reflected by elevated expression of the gene that encodes the transcription factor c-Fos, decreases significantly with age (73).

Because POMC reduces body weight independently of food intake (66), these impairments in POMC neurons may contribute to increased body weight by reducing the metabolic rate during aging. Because feeding-induced activation of POMC neurons is independent of leptin (74), these data suggest that hypothalamic responses to some other nutritional factor decline during aging. Indeed, although sensitivity to leptin injected intraperitoneally declines in mice between 2 and 11 months of age (57), we have observed that 6- and 22-month-old mice lose a similar amount of body weight when they receive daily injections of leptin for 5 days (38). In contrast, glucose reduces food intake more effectively in 24-month-old than in 12-month-old mice (73). A similarly impaired anorectic response to glucose was observed in diabetic mice; furthermore, feeding-induced activation of POMC neurons was reduced in diabetic mice (73). These data suggest that a cumulative effect of glucose could produce impairments in responsiveness of POMC to glucose or some factor acutely induced by feeding (for example, insulin). Such a phenomenon would be consistent with the proposal that cumulative toxic effects of glucose cause neuroendocrine impairments, including obesity (75).

As indicated above, although adiposity usually increases until late middle age, it begins to decrease thereafter. Thus, just as the age-related increase in adiposity (through late middle age) must be explained, so too must the senescent decrease in adiposity. Indeed, it could be argued that the loss of adiposity is more characteristic of senescence in the usual sense than is the increase in adiposity from young adulthood to late middle age. Although the age-related increased adiposity is actively defended through late middle age, later in life this defense of body weight becomes attenuated, just as body adiposity begins to de-

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**Fig. 2.** (A) Key tissues that mediate the effects of leptin on body weight. Leptin is synthesized in fat in response to nutritional stimulation. The effects of leptin are mediated through hypothalamic neurons, especially POMC and corticotropin-releasing factor (CRH) neurons, which express leptin receptors. POMC neurons, which are also stimulated by other factors including glucose, activate the sympathetic nervous system. Leptin also reduces the activity of the hypothalamic-pituitary-adrenal gland axis, ultimately leading to a reduction in glucocorticoid secretion. ACTH, adrenocorticotropic hormone. (B) Leptin acts on the leptin receptor, a member of the cytokine receptor family, which in turn activates the STAT3 transcription factor by phosphorylation via the JAK2 kinase. Upon activation and dimerization, STAT3 enters the nucleus to regulate gene expression, including the expression of POMC.
increase. Therefore, the senescent decline in body weight could result from a loss of responsiveness to nutritional deficiency. In turn, as with the age-related increase in adiposity, the age-related decline in responsiveness to nutritional perturbation in late life (27-29) could result from impairments in hypothalamic responses to nutritional signals. For example, induction of hypothalamic neuropeptide Y in response to food deprivation is attenuated in relatively old rats (53, 71, 76) compared to relatively young rats. However, hypothalamic responses to fasting are very similar in 6-month-old and 24-month-old mice (38). Because failure to defend body weight is observed mainly in late life (27-29), these data do not support the hypothesis that impaired hypothalamic responses to fasting are the cause of impaired defense of body weight in advanced old age. Nevertheless, other hypothalamic responses to fasting that have not yet been examined could explain these impairments.

In conclusion, obesity generally increases up until middle age and decreases thereafter. Furthermore, obesity in middle-aged humans decreases life expectancy by about 7 years, which is roughly comparable to the combined effects of cardiovascular disease and all cancers. Unlike cardiovascular disease and cancer, however, the deleterious effects of obesity appear to decline after late middle age. These data suggest that effects of obesity on life expectancy occur through mechanisms mediated primarily before late middle age. After late middle age, adiposity usually decreases, and low BMI becomes a risk factor for mortality. Mechanisms that lead to increased, then decreased, body weight with age are not yet well understood, but the current evidence suggests impairments in hypothalamic function, especially in the ability of POMC neurons to sense nutritional stimulation. The rapid increase in the prevalence of obesity at all ages seen in the past decade in the United States and other developed countries suggests that in the next two or three decades, diseases associated with obesity, especially diabetes, will begin to rise rapidly. Because obesity is so deleterious, it is possible that the current rapid rise in obesity may, for the first time in modern history, produce a reduction in life expectancy. Therefore, more research on the causes and consequences of obesity during aging is urgently needed.

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