REVIEW OF LITERATURE
3. REVIEW OF LITERATURE

3.1. OBESITY

Obesity is an abnormal accumulation of fat in proportion to body size. It is a major public health and economic problem of global significance. Prevalence rates are increasing in all parts of the world, both in developed and developing countries. Men, women and children are affected. Undeniably, overweight, obesity and health problems associated with them are now so common that they are replacing the more traditional public health concerns such as under nutrition and infectious disease as the most significant contributors to global ill health\(^{(18)}\). In 1995, the excess adult mortality attributable to over nutrition was estimated to be about 1 million deaths, double the 0.5 million attributable to under nutrition\(^{(19)}\).

The prevalence of obesity exceeds 30% in adults and is associated with increased risk of such serious health problems as, type 2 diabetes, cardiovascular diseases and various types of cancer. These comorbid conditions are associated with greater use of health care services among obese patients\(^{(20,21)}\) (Table 3.1).

Table 3.1: Consequences of obesity

<table>
<thead>
<tr>
<th>Physical</th>
<th>Psychosocial</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Depression</td>
<td>Absenteeism from School</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Discrimination</td>
<td>or work</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Low self-esteem</td>
<td>Disability</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Negative body image</td>
<td>Disqualification from active</td>
</tr>
<tr>
<td>Gall bladder disease</td>
<td>Negative stereotyping</td>
<td>military/fire/police services</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>Social marginalization</td>
<td>Low physical fitness</td>
</tr>
<tr>
<td>and Insulin resistance</td>
<td>Stigma</td>
<td>Mobility limitations</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>Teasing and bullying</td>
<td>Reduced academic</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>performance</td>
</tr>
<tr>
<td>Hyperuricemia and gout</td>
<td></td>
<td>Reduced productivity</td>
</tr>
<tr>
<td>Menstrual abnormalities</td>
<td></td>
<td>Unemployment</td>
</tr>
<tr>
<td>Orthopedic problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of cerebral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep apnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evaluation of *Caralluma fimbriata* extract in animal models of obesity

Obesity is also associated with an increased risk of premature death in adults <65 years. The leading causes of death in obese adults include diabetes, ischemic heart disease, respiratory diseases, and cancer (i.e., liver, kidney, breast, endometrial, prostate, and colon). Weight loss in obese individuals is associated with a lower incidence of health problems and a reduced risk of premature death\(^\text{(20)}\).

### 3.2. EPIDEMIOLOGY AND IMPACT

Between 1988 and 2008, the prevalence of obesity increased in adults of all income and education levels. However, women with limited education and lower incomes tend to be at greater risk of obesity. Similarly, obesity affects some racial and ethnic groups more than others. Non-Hispanic blacks have the highest age adjusted rates of obesity (49.5%), compared with Mexican Americans (40.4%), all Hispanics (39.1%), and non-Hispanic whites (34.3%)\(^\text{(22)}\). The prevalence of obesity among children and adolescents has also increased, almost tripling since 2000. Approximately 17% of children and adolescents ages 2 to 19 years are obese\(^\text{(23)}\) There is some reason for optimism, however. Among children ages 2 to 4 years in low-income households, the prevalence of obesity and extreme obesity appear to have decreased slightly between 2003 and 2010\(^\text{(23,24)}\). As with adults, there are significant racial and ethnic disparities in obesity prevalence among children and adolescents. Hispanic boys are significantly more likely to be obese than non-Hispanic white boys, and non-Hispanic black girls are significantly more likely to be obese than their non-Hispanic white peers.

### 3.3. THE GLOBAL OBESITY PROBLEM

The number of people worldwide with a BMI of 30 or above is currently thought to exceed 250 million, i.e. 7% of the world’s adult population (Table 3.2)\(^\text{(25)}\). When individual countries are considered, the range of obesity prevalence covers almost the full spectrum, from below 5% in China, Japan and certain African nations to more than 75% in urban Samoa. It is difficult to calculate an exact global figure because good quality and comparable data are not widely available. The assessment in Table 3.2 is a conservative estimate.
At the physiological level, obesity can be defined as a condition of abnormal or excessive fat accumulation in adipose tissue to the extent that health may be impaired. However, it is difficult to measure body fat directly and so surrogate measures such as the body mass index (BMI) are commonly used to indicate overweight and obesity in adults. Additional tools are available for identification of individuals with increased health risks due to ‘central’ fat distribution, and for the more detailed characterization of excess fat in special clinical situations and research.

### 3.4. CLASSIFICATION OF OBESITY

#### 3.4.1. BODY MASS INDEX

Body mass index (BMI), which is calculated by dividing the body weight in kilograms by height in meters squared, is a classification system that attempts to allow comparison of weights independent of stature across populations. Except in persons who have increased lean weight as a result of intense exercise (e.g., body builders), BMI does not correlate with percentage body fat, but this relationship is independently influenced by sex, age and race.

The BMI provides the most useful and practical population-level indicator of overweight and obesity in adults. It is calculated by dividing bodyweight in kilograms by height in metres squared (BMI kg/m$^2$). Both height and weight are routinely collected in clinical and population health surveys. In the new graded classification system developed by the World Health Organization (WHO), a BMI of 30 kg/m$^2$ or above denotes obesity (Table 3.2: Estimated world prevalence of obesity).

<table>
<thead>
<tr>
<th>Country</th>
<th>Population aged ≥15 years (millions)</th>
<th>Prevalence of obesity (%)</th>
<th>Approximate estimate (mid-point) of number of obese individuals (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established market economies</td>
<td>640</td>
<td>15–20</td>
<td>95–128</td>
</tr>
<tr>
<td>Former socialist economies</td>
<td>330</td>
<td>20–25</td>
<td>66–83</td>
</tr>
<tr>
<td>India</td>
<td>535</td>
<td>0.5–1.0</td>
<td>3–7</td>
</tr>
<tr>
<td>China</td>
<td>825</td>
<td>0.5–1.0</td>
<td>4–8</td>
</tr>
<tr>
<td>Other Asian countries and Islands</td>
<td>430</td>
<td>1–3</td>
<td>4–12</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>276</td>
<td>0.5–1.0</td>
<td>1–3</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>280</td>
<td>5–10</td>
<td>14–28</td>
</tr>
<tr>
<td>Middle East</td>
<td>300</td>
<td>5–10</td>
<td>15–30</td>
</tr>
<tr>
<td>World</td>
<td>3616</td>
<td></td>
<td>(251)</td>
</tr>
</tbody>
</table>

Source: Seidell (26)
There is a high likelihood that individuals with a BMI at or above this level will have excessive body fat. However, the health risks associated with overweight and obesity appear to rise progressively with increasing BMI from a value below 25 kg/m², and it has been demonstrated that there are benefits to having a measurement nearer 20-22 kg/m², at least within industrialized countries. To highlight the health risks that can exist at BMI values below the level of obesity, and to raise awareness of the need to prevent further weight gain beyond this level, the first category of overweight included in the new WHO classification system is termed ‘preobese’ (BMI 25—29.9 kg/m²).

Table 3.3 Classification of overweight and obesity in adults according to BMI

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obese Class I</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Obese Class II</td>
<td>35-39.9</td>
</tr>
<tr>
<td>Obese Class III</td>
<td>≥40</td>
</tr>
</tbody>
</table>

Source: WHO\(^{(18)}\)

Caution is required when interpreting BMI measurements in certain individuals and ethnic groups. The relationship between BMI and body fat content varies according to body build and body proportion, and a given BMI may not correspond to the same degree of fatness across all populations. Recently, a meta-analysis among different ethnic groups showed that for the same level of body fat, age and gender, American blacks have a 1.3 kg/m² higher BMI and Polynesians have a 4.5 kg/m² higher BMI compared to Caucasians. By contrast, BMIs in Chinese, Ethiopians, Indonesians and Thais were shown to be 1.9, 4.6, 3.2 and 2.9 kg/m² lower than in Caucasians\(^{(26)}\). This suggests that population-specific BMI cut-off points for obesity need to be developed.

3.5. ETIOLOGY AND GENETICS

Studies of populations, families, adoptions and twins have established a strong genetic role in determining body weight. Estimates of the genetic contribution to the variance of
relative body weight and adiposity range from a low of approximately 30% to a high of 90%. The largest study to address the contribution of nature versus nurture to body weight, which used a dataset that included over 25000 twin pairs and 50000 biologic and adoptive family members, found that genetic factors accounted for 67% of the variance in adiposity in men and women. Rarely childhood-onset obesity will manifest itself as a result of a single-gene obesity syndrome, such as Prader Willi syndrome or Bartlett-Biedel syndrome, or from a mutation in one of the genes encoding proteins involved with body weight regulation, such as the pro-opiomelanocortin (POMC) gene, which makes α-melanocortin-stimulating hormone (α-MSH); the melanocortin receptor (MC4), leptin; the leptin receptor and prohormone convertase enzymes.

Although the genetics explaining the tendency toward overweight and obesity in majority of the population remains to be elucidated, over 600 genetic markers have been described in association with obesity-related variables in humans (eg., BMI, skin fold thickness, waist–to-hip ratio, fat mass and percent fat mass). With time, discoveries of specific gene products, the role that these proteins play in the pathophysiology of weight regulation and their interaction with the environment in the expression of unwanted weight gain should lead to more specific pharmacologic treatments for overweight and obese patients who fail to respond adequately to lifestyle measures alone.

Epidemiological studies have identified several environmental factors that contribute to the continued weight gain documented over the past several decades in westernized countries. The foremost among these factors are an increasingly sedentary lifestyle (eg., increased car use, work environments and community that discourage activity, and more time to spend watching television) and the availability of energy-dense (high fat, concentrated sugar) low fiber foods. In children the increased consumption of sugar added beverages and reduction of dairy intake have also been associated with greater weight gain in prospective studies. Similar environmental predictors of weight gain have been described in societies adopting Western lifestyles in the transition to First World economies. Additional societal trends that are thought to have contributed to the increasing weight gain in the United States include smoking cessation (cigarette smoking...
is known to reduce body weight\textsuperscript{(31,32)} and eating a greater proportion of food away from home, particularly at fast food restaurants, where food is typically calorically dense.

3.6. PATHOPHYSIOLOGY AND PATHOGENESIS

Arguably the most significant recent advances in the science of obesity have been in the area of neuroendocrine control of energy homeostasis, including the understanding of the mechanisms that lead to unwanted weight gain and the counter regulatory systems that restore weight loss after caloric restriction. At its most basic level, body weight is end result of a balance between energy uptake and its expenditure. Weight loss occurs through restriction of energy intake, increased energy output or both.

Like glucose, body weight is regulated at multiple levels to maintain a normal range or set point through an interaction between systems that control meal to meal intake (satiety) and those that control relative fat mass (adiposity) [see Figure 3.1\textsuperscript{(33)} although short term (meal to meal) signals such as cholecystokinin have been studied for decades, a long term afferent signal from fat tissue, leptin was not discovered until 1994\textsuperscript{(34)}. Leptin is a hormone that is secreted by fat cells in direct proportion to total fat mass, is transported across the blood brain barrier and has receptors in hypothalamic nuclei that control appetite and energy expenditure. When leptin levels decline with weight loss from caloric restriction or when they increase with overfeeding, altered signaling in central hypothalamic centers become integrated with other input signals (e.g., insulin and ghrelin) to set in motion systems that restore body weight to baseline. Therefore most obese patients fail to sustain long term weight loss with calorie restriction alone because of activation of these counter regulatory systems and their promotion of positive energy balance. Future medical therapies will be based on an understanding of the body’s weight regulatory system and will have greater promise for success in maintain weight loss.

With aging, deregulation of a number of hypothalamic-pituitary systems may contribute to increased fat mass and sarcopenia. For example growth hormone secretion diminishes with age. Prospective trials in older adults that involved replacing growth hormone and targeting levels of insulin like growth factor -1 (IGF-1) to the mid normal to upper-normal range have demonstrated improved body composition (less fat, more lean tissue)
and in some studies reduced central fat\(^{35-37}\). In addition, the decline in testosterone levels in men, the reduction in estrogen levels in women at menopause and increased levels of cortisol in both sexes may also contribute to reduced muscle mass, central distribution of fat or both.

Figure 3.1: A feed back model for body weight regulation in humans based on data from animals\(^{(33)}\)

3.7. ENERGY METABOLISM

The components of daily total energy expenditure (TEE) are:

1. Resting energy expenditure (REE), accounting for approximately 70% of TEE.
2. Energy expended in physical activity, accounting for approximately 20% of TEE.
3. The thermic effect of food (TEF), accounting for approximately 10% of TEE.

REE represents the energy expended for normal cellular and organ function under postabsorptive resting conditions. Energy expended in physical activity includes the
energy costs of both volitional activity, such as exercise, and non-volitional activity, such as spontaneous muscle contractions, maintaining posture, and fidgeting.

The thermic effect of food represents the energy expended in digestion, absorption, and sympathetic nervous system activation after ingestion of a meal. Cross-sectional studies have investigated whether alterations in energy metabolism are involved in obesity. Obese individuals usually have greater rates of REE than lean individuals of the same height because obese individuals have a greater amount of lean and adipose tissue cell mass\(^{(38)}\). Defects in REE or TEE have not been detected in diet-resistant patients who maintain their weight despite the claim of strict adherence to a low-calorie diet\(^{(39)}\). Instead, such patients appear to underestimate their food intake and actually consume twice as many calories as they record in food intake diaries. It is not known whether obese individuals expend less total energy in daily physical activity because they are less active than lean individuals. During non weight-bearing activity (e.g., cycling), obese individuals expend the same amount of energy as lean individuals to perform the same amount of work. During weight-bearing activities, however, obese individuals expend more energy than lean individuals because more work is required to carry their greater body weight. Evidence from studies of obese and lean subjects, matched for either fat mass or lean body mass, suggests that obese subjects have a small (75 kcal/day) but potentially important reduction in the thermic effect of food\(^{(40)}\). This reduction in the thermic effect of food may arise from the insulin resistance and blunted sympathetic nervous system activity that occur in obesity\(^{(41)}\). Although extensive research has not revealed significant defects in the energy metabolism of individuals who are already obese, the possibility remains that inherent abnormalities in energy metabolism contribute to the development of obesity. However, today's research technology has only limited ability to detect small, but possibly clinically significant, chronic defects in energy metabolism. Moreover, it is difficult to establish a causal relationship between energy expenditure and the development of obesity because energy metabolism measurements capture only a brief point in time and may not reveal abnormalities that emerge during specific life stages.
Most studies do not support the involvement of a defect in metabolic rate in the development of obesity. In one longitudinal study, daily TEE at 3 months of age was 21% lower in infants who later became overweight than in those who maintained a normal weight\(^{(42)}\). However, larger subsequent studies\(^{(43)}\) have not confirmed this finding. In a longitudinal study of 126 Pima Indians, those in the lowest tertile of REE at baseline had the highest cumulative incidence of a 10-kg weight gain 1 to 4 years later\(^{(44)}\). In contrast, the Baltimore Longitudinal Study on Aging, which monitored 775 men for an average of 10 years, did not detect a relationship between initial REE and weight change\(^{(45)}\). When energy intake exceeds energy expenditure, weight gain usually occurs. However, genetic factors may influence the amount of weight gained with overfeeding. Bouchard and colleagues\(^{(46)}\) observed variable weight gain among 12 monozygotic twin pairs who were chronically overfed 1000 kcal/day. However, the members of each twin pair gained similar amounts of weight. In another study, the increase in body fat after 8 weeks of overfeeding was inversely related to changes in non-volitional energy expenditure (e.g., fidgeting)\(^{(47)}\). Therefore, in some individuals, non-volitional energy expenditure during periods of over ingestion could be a mechanism that limits weight gain through the dissipation of excess ingested energy. Diet-induced weight loss decreases REE, which promotes weight regain. This observation underlies the set-point theory, which posits that body weight is predetermined so that weight loss (or gain) promotes a decrease (or increase) in metabolic rate that acts to restore body weight to a preset level. In both lean and obese persons, hypocaloric feeding reduces REE by 15% to 30%. This reduction in REE cannot be completely accounted for by the accompanying decrease in body size or lean body mass and is considered a normal part of the physiologic adaptation to energy restriction\(^{(48)}\). The reduction in REE that occurs with negative energy balance is transient and does not persist during maintenance of a lower body weight. As reported in several studies, long-term maintenance of weight loss is not associated with an abnormal decrease in REE or TEE when adjustments are made for changes in body composition\(^{(49)}\). In a meta-analysis of 15 studies, the REE of subjects who were formerly obese was found to be similar to that of subjects who were never obese\(^{(50)}\). Although the decrease in energy metabolism with weight loss is largely
appropriate for the concomitant changes in body composition, this decrease may nonetheless promote weight regain.

3.8. ADIPOSE TISSUE AND TRIGLYCERIDE METABOLISM

Triglycerides stored within adipose tissue constitute the body's major energy reserve (Table 3.4). Triglycerides are a much more compact fuel than glycogen because of their energy density and hydrophobic nature. Triglycerides yield 9.3 kcal/g upon oxidation and are compactly stored as oil inside the fat cell, accounting for 85% of adipocyte weight. Glycogen, in contrast, yields only 4.1 kcal/g upon oxidation and is stored intracellularly as a gel containing approximately 2 g of water for every gram of glycogen. Adipose tissue is an effective storage mechanism for transportable fuel that allows mobility and survival when food is scarce. During starvation, the duration of survival is determined by the size of the adipose tissue mass. Lean persons die after only approximately 60 days of starvation when more than 35% of body weight is lost. Obese persons, in contrast, have tolerated therapeutic fasts for more than a year without adverse effects. In the longest reported fast, a 207-kg man ingested only non-caloric fluids, vitamins, and minerals for 382 days and lost 126 kg, or 61% of his initial weight\(^{(51)}\).

Table 3.4: Endogenous fuel stores in a man weighing 70 kg\(^{(51)}\)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Fuel Source</th>
<th>Mass Grams</th>
<th>Mass Kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose tissue</td>
<td>Triglyceride</td>
<td>13,000</td>
<td>120,000</td>
</tr>
<tr>
<td>Liver</td>
<td>Glycogen</td>
<td>100</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>50</td>
<td>450</td>
</tr>
<tr>
<td>Muscle</td>
<td>Glycogen</td>
<td>500</td>
<td>2,000</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>300</td>
<td>2,700</td>
</tr>
<tr>
<td>Blood</td>
<td>Glucose</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Free fatty acids</td>
<td>0.5</td>
<td>5</td>
</tr>
</tbody>
</table>

3.8.1. Triglyceride Storage

The major function of adipocytes is the storage of triglycerides for future use as energy substrate. Lipogenesis from glucose makes only a limited contribution to triglyceride storage in the adipocyte\(^{(51)}\). Most of the triglyceride in adipocytes is derived from chylomicrons and very-low-density lipoprotein (VLDL) triglycerides that originate,
respectively, from dietary and hepatic sources. These plasma triglycerides are hydrolyzed by lipoprotein lipase (LPL), a key regulator of fat cell triglyceride uptake from circulating triglycerides. LPL is synthesized by adipocytes and transported to the endoluminal surface of endothelial cells. The interactions of LPL with chylomicrons and VLDL release fatty acids from plasma triglycerides, which are then taken up by local adipocytes. Plasma free fatty acids themselves can also be taken up by adipose tissue, independent of lipoprotein lipolysis. Insulin and cortisol are the principal hormones involved in regulation of LPL activity and expression. The activity of LPL within individual tissues is a key factor in partitioning triglycerides among different body tissues. Insulin influences this partitioning through its stimulation of LPL activity in adipose tissue. Insulin also promotes triglyceride storage in adipocytes through other mechanisms, including inhibition of lipolysis, stimulation of adipocyte differentiation, and increasing glucose uptake. The importance of cortisol in fat distribution is supported by the clinical appearance of patients with Cushing's syndrome. The obesity-promoting effect of cortisol may involve a synergistic effect of cortisol and insulin on the induction of LPL in adipose tissue, which has been demonstrated in vitro. Testosterone, growth hormone, catecholamines, and tumor necrosis factor (TNF) and other related cytokines inhibit LPL activity.

3.8.2. Lipolysis

The balance between triglyceride storage and lipolysis is regulated by complex hormonal and neuronal mechanisms. To become available as an energy substrate, triglycerides stored within adipocytes must be hydrolyzed by hormone-sensitive lipase into fatty acids. These fatty acids can be released from adipocytes into the circulation. The circulating half-life of plasma fatty acids is only 3 to 4 minutes. Under resting conditions, fatty acid release by adipose tissue exceeds the rate of fatty acid oxidation\(^\text{(52)}\). The excess availability of fatty acids in plasma provides a ready supply of oxidizable substrate to respond to sudden changes in energy requirements, such as are induced by exercise. The plasma fatty acids that escape immediate oxidation are usually re-esterified to triglyceride in adipose tissue, muscle, or liver. These fatty acids are the major precursors of hepatic VLDL triglyceride synthesis. In turn, VLDL triglycerides are secreted by the liver and
redistributed throughout the body, depending on tissue-specific factors such as the activity of LPL. These observations imply that there is continuous redistribution of triglycerides between adipose tissue and the rest of the body. There is considerable variation in the rate of lipolysis and, consequently, plasma fatty acid level both within and between subjects. Insulin and catecholamines are the major circulating hormones that influence lipolysis in adipocytes. Insulin inhibits lipolysis through its effect on hormone-sensitive lipase, whereas catecholamines stimulate lipolysis. Small changes in the plasma concentrations of insulin and catecholamines have major effects on lipolytic rate. Half-maximal suppression of lipolysis occurs at post absorptive insulin levels, and maximal suppression of lipolysis occurs at insulin levels within the range observed after a regular meal. Only minor increases in resting catecholamine levels stimulate lipolysis. Other factors modulate the rate of lipolysis. For example, growth hormone and cortisol stimulate lipolysis. In general, the effects of these other factors are less potent than the effects of insulin and catecholamines. In contrast to the tight feedback regulation of insulin secretion by glucose levels, insulin and catecholamine concentrations are not regulated by lipolysis or fatty acid levels. Although free fatty acid levels affect glucose-stimulated insulin release, there is no feedback between insulin release and rate of lipolysis. The wide physiologic variation in plasma free fatty acid concentrations between individuals can be explained, in part, by the finely tuned dose-response effects of insulin and catecholamines on lipolysis in combination with the absence of tight feedback regulation of insulin and catecholamine levels by free fatty acids. Basal plasma fatty acid concentrations are often increased in obese persons, particularly those with abdominal (upper body) obesity. An increased rate of free fatty acid release into plasma because of an increased rate of lipolysis from upper body subcutaneous fat is responsible for the higher levels of circulating fatty acids. The excess free fatty acid availability in plasma may lead to increased hepatic free fatty acid uptake, VLDL triglyceride synthesis, intramuscular triglyceride formation, and insulin resistance.

3.8.3. Adipocyte biology

Obesity is associated with an increased number of adipocytes. A lean adult has about 35 billion adipocytes, each containing about 0.4 to 0.6 μg of triglyceride; an extremely obese
adult can have four times as many adipocytes (125 billion), each containing twice as much lipid (0.8 to 1.2 μg of triglyceride). Our understanding of adipocyte differentiation is largely derived from studies of preadipocytes in culture. The current concept is that adipocytes are derived from fibroblast precursor cells after the concerted actions of extracellular signals and intrinsic transcription factors and co-activators. Many extranuclear factors and intracellular transduction pathways influence the adipogenic potential of cells in vitro and in vivo. Although in the future it may be possible to regulate adipogenesis in vivo, decreasing adipogenesis without altering energy balance may result in the deposition of triglycerides in other tissues. Excessive triglycerides in nonadipose tissues can have deleterious effects, as suggested by the liver steatosis, dyslipidemia, and diabetes observed when adipogenesis was prevented in mice.53

The cornerstone of obesity therapy is to increase the utilization of endogenous fat stores as fuel by reducing energy intake below energy expenditure. With dieting, weight loss is composed of approximately 75% to 85% fat and 15% to 25% fat free mass (FFM). An energy deficit of approximately 3500 kcal is required to oxidize 1 pound of adipose tissue. However, because of the oxidation of lean tissue and associated water losses, a 3500-kcal energy deficit reduces body weight by more than 1 pound. The distribution of fat loss is characterized by regional heterogeneity. Particularly in men and women with initially increased intra-abdominal fat, there are greater relative losses of intra-abdominal fat than of total body fat mass. A decrease in the size (triglyceride content) of existing adipocytes accounts for most, if not all, of the fat loss. In humans, there is also evidence that the number of adipocytes is reduced with large, long-term fat loss. However, it is possible that this perception of decreased fat cell number is false because standard cell-counting techniques may fail to detect adipocytes that have undergone marked shrinkage.

3.8.4. Adipose tissue as an endocrine organ

Traditionally, adipocytes have been viewed as energy depots that store triglycerides during feeding and release fatty acids during fasting to provide fuel for other tissues. However, it has become evident that adipose tissue has major integrative physiologic functions and secretes numerous proteins (Table 3.5)54. In part, these factors participate in autocrine and paracrine regulation within adipose tissue. In addition, these factors have
profound effects on the function of distant organs, such as muscle, pancreas, liver, and brain. The realization that adipose tissue functions as an endocrine organ has important implications for understanding the pathophysiologic relationship between excess body fat and pathologic states, such as insulin resistance and type 2 diabetes mellitus.

Table 3.5: Adipocyte Secreted Proteins

<table>
<thead>
<tr>
<th>Category</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential Hormone</td>
<td>Leptin, resistin, angiotensinogen, Adiponectin/ACRP 30, estrogens</td>
</tr>
<tr>
<td>Cytokine</td>
<td>Interleukin-B tumor necrosis factor</td>
</tr>
<tr>
<td>Extracellular matrix protein</td>
<td>Type I,III,IV and VI collagen, fibronectin, osteonecin, laminin, entactin, matrix metaloproteinases 2 and 9</td>
</tr>
<tr>
<td>Complement factor</td>
<td>Adipsin, complement C3,factor B</td>
</tr>
<tr>
<td>Enzyme</td>
<td>Cholester ester transfer protein, lipoprotein lipase</td>
</tr>
<tr>
<td>Acute phase response</td>
<td>1- Acid glycoprotein, haptoglobin</td>
</tr>
<tr>
<td>Other</td>
<td>Fatty acids</td>
</tr>
<tr>
<td></td>
<td>Plasminogen activator inhibitor-1</td>
</tr>
<tr>
<td></td>
<td>Prostacyclin</td>
</tr>
</tbody>
</table>

3.8.4.1. Leptin

Adipocytes produce leptin and secrete it into the blood stream. Leptin has pleiotropic effects on food intake, hypothalamic neuroendocrine regulation, reproductive function, and energy expenditure. There is a direct relationship between plasma leptin concentrations and BMI or percent body fat. However, there can be considerable variability in leptin concentrations among persons with the same BMI, suggesting that leptin production is also regulated by factors other than adipose tissue mass per se. Leptin levels decrease rapidly within 12 hours after the start of starvation; conversely, they increase in response to overfeeding. Therefore, plasma leptin concentrations reflect adipose tissue mass and are influenced by energy balance. In this perspective, leptin is a bidirectional signal that switches physiologic regulation between fed and starved states. Plasma leptin concentrations increase with increasing fat mass and decrease rapidly
during early fasting. At present, the relative importance of the central versus peripheral effects of leptin remains to be elucidated.

3.8.4.2. Resistin

Resistin is another signaling polypeptide secreted by adipocytes. Resistin levels are increased in mice with diet-induced and genetic forms of obesity and insulin resistance. Administration of recombinant resistin to normal mice impaired glucose tolerance and insulin action. Neutralization of resistin reduced hyperglycemia in obese, insulin-resistant mice, in part by improving insulin sensitivity. It has therefore been proposed that resistin is a hormone that links obesity to diabetes by inducing insulin resistance.

3.8.4.2. Estrogens

Adipose tissue has aromatase activity. This enzyme is important for transforming androstenedione into estrone. Estrone is the second major circulating estrogen in premenopausal women and the most important estrogen in postmenopausal women. The rate of conversion of androstenedione to estrone increases with age and obesity and is higher in lower body than in upper body obesity. In addition to a role in endocrine regulation, the effects of P450 aromatase on estrogen metabolism may have a role in autocrine or paracrine action because estrogen receptors are present in adipose tissue.

3.8.4.3. Tumor Necrosis Factor

Adipocytes secrete TNF-, and TNF- expression is increased in the enlarged adipocytes of obese subjects. However, plasma TNF- levels are generally at or below the detection limit of available assays, which suggests that the TNF- produced within adipose tissue has paracrine rather than endocrine functions. The multiple effects of TNF- on adipocytes include impairment of insulin signaling. Therefore, it has been proposed that TNF- may partially contribute to insulin resistance in obesity.

There are two possible mechanisms through which weight loss can eliminate fat cells: (1) dedifferentiation, the morphologic and biochemical reversion of mature adipocytes to preadipocytes, and (2) apoptosis. Adipocyte dedifferentiation has been observed in vitro, but there is no evidence that it occurs in vivo. Adipocyte apoptosis has been induced in
vitro and has been shown to occur in vivo in some patients with cancer. To date, it is not known whether diet-mediated weight loss induces adipocyte apoptosis.

**Interrelationships between Hypothalamic Neuropeptides and Leptin in the Maintenance of Body Weight Homeostasis, or Evolution to Obesity**

It is now accepted that body weight homeostasis is maintained via a series of complex interactions that occur between the brain, the hypothalamus in particular, and the periphery, notably via a hormone, leptin, synthesized in and secreted from adipose tissue\(^{(55)}\). Secreted leptin, although it may have direct peripheral effects, exerts its action principally within the brain. Following its transport through the blood—brain barrier, possibly via the short leptin receptor isoform (ObRa), leptin reaches the hypothalamic area where it binds to its long receptor isoform (ObRb). Following a specific signaling cascade, leptin inhibits many of the orexigenic neuropeptides, while favoring many of the anorexigenic ones, as discussed below. By doing so, leptin exerts its effects of decreasing food intake and body weight, increasing fat oxidation and energy expenditure, thus favoring leanness\(^{(56)}\). In the present review, the characteristics of the main orexigenic and anorexigenic neuropeptides will be summarized (Figure 3.2) and putative effects of leptin thereon described or, when such effects of leptin are defective, the main reasons for the establishment of a state of obesity will be outlined (Figure 3.3).

**3.9. OREXIGENIC NEUROPEPTIDES**

**3.9.1. Effects of Neuropeptide Y (NPY)**

NPY is a 36 amino acid neuropeptide that is widely distributed in the brain. In the hypothalamus, it is synthesized in the arcuate nucleus and released in the paraventricular nucleus. It stimulates food intake by binding to Y1 and/or Y5 receptor subtypes\(^{(57,58)}\). This increase in feeding can be observed upon infusing the peptide intracerebroventricularly (i.c.v.) in normal rats and is accompanied by a rapid, sustained and marked increase in body weight. Central NPY infusion also stimulates insulin secretion via an activation of the parasympathetic nervous system reaching the endocrine pancreas. Concomitantly, central NPY administration increases the activity of the hypothalampituitary-adrenal axis, with resulting hypercorticosteronemia and increased
susceptibility to stressful situations\(^{(59)}\). Finally, central NPY reduces the activity of the efferent sympathetic nerves reaching brown adipose tissue, with resulting decrease in energy dissipation as heat\(^{(60,61)}\). The metabolic consequences of the hormonal changes produced by central NPY infusion (increased plasma insulin and corticosterone levels) are increased adipose tissue and liver lipogenic activity, changes mainly due to hyperinsulinemia\(^{(59,62)}\), together with decreased insulin-stimulated glucose utilization by muscles. This muscle insulin resistance is likely to be due to the combined NPY-induced hyperinsulinemia/hypercorticosteronemia. It should be noted that the NPY-elicited effects are very marked when exogenous NPY is chronically infused i.c.v., resulting in high central concentrations of the neuropeptide. Physiologically, however, it is thought that these changes are modest, occurring via the spontaneous fluctuations of hypothalamic NPY levels, which transiently change nutrient partitioning toward fat accretion and decreased oxidation processes. This situation persists until leptin is secreted into the blood as a result of hormonal changes such as transient hyperinsulinemia in response to meal taking. Secreted leptin reaches the brain and decreases hypothalamic NPY levels by exerting its negative feedback inhibition on the expression and amount of this neuropeptide\(^{(63,64)}\). Experiments have shown, however, that in addition to NPY, other brain neuropeptidic systems play a role in the regulation of food intake. Thus, in transgenic mice made deficient in NPY, the expected decrease in both food intake and body weight fails to occur\(^{(65,66)}\). Transgenic mice lacking the NPY-Y1 or Y5 receptor actually gain more weight, not less, than the controls\(^{(67)}\). This indicates that the regulation of food intake and body weight is redundant, i.e. that several pathways are implicated and that when one of them is knocked out, others take over to maintain a normal body weight homeostasis.
Figure 3.2: Diagram of food intake regulation by orexigenic and anorexigenic neuropeptides

Figure 3.3: Diagram of the central effects of leptin on food intake

3.9.2. NPY and Obesity

When considering the hormono-metabolic changes produced by central NPY, one realizes that experimentally produced increases in central levels of this neuropeptide reproduce most of the abnormalities observed in experimental or genetic obesity.
Evaluation of Caralluma fimbriata extract in animal models of obesity

syndromes\textsuperscript{(59,62)}, as well as in human obesity. The pathological relevance of increased hypothalamic NPY levels in mimicking obesity syndromes is supported by the observation that NPY expression and levels are indeed increased in the ob/ob, db/db obese mice and in the fa/fa obese rat\textsuperscript{(63,64)}. Increased NPY levels in ob/ob mice are due to the lack of synthesis and secretion of leptin in adipose tissue, the ob (leptin) gene being mutated. As a result of this mutation, plasma leptin levels are nil, leptin fails to exert its negative feedback on hypothalamic NPY levels which remain continually elevated maintaining, probably with other neuropeptides that are influenced by leptin, the obesity syndrome\textsuperscript{(68)}. In the db/db and the fa/fa obese rodents, the ob gene of adipose tissue is normal, but the long form leptin receptor is mutated in its intracellular (db/db)\textsuperscript{(56)} or extracellular (fa/fa)\textsuperscript{(69)} domain. Even though leptin is overproduced by adipose tissue, bringing about a state of hyperleptinemia, it cannot act centrally and hypothalamic NPY levels remain high. The latter, probably in concert with other neuropeptides, maintain the obesity syndrome\textsuperscript{(70)}.

3.9.3. Effects of Melanin Concentrating Hormone (MCH)

MCH is a cyclic neuropeptide comprising 19 amino acids which is present in many areas of the brain, notably in the lateral hypothalamus\textsuperscript{(71)}. Its name derives from its ability to cause melanosome aggregation in fish skin, an action which is antagonized by α-MSH, the melanosome-dispersing factor. Recently, a role for MCH in the central regulation of food intake has been discovered, intracerebroventricular (i.c.v). MCH administration increasing food intake in normal rats\textsuperscript{(72,73)}. As for the melanosome aggregation/dispersion system, the action of α-MSH is the opposite of that of MCH, resulting in decreased food intake. The antagonistic action of MCH and α-MSH extends to the regulation of the hypothalamo-pituitary-adrenal (HPA) axis, MCH decreasing plasma corticosterone and ACTH levels relative to controls, while α-MSH does the contrary, increasing plasma corticosterone and ACTH levels. i.c.v. administration of a single dose of MCH results in stimulation of food intake that is dose dependent, lasts for about 6 hours, but is moderate in amplitude when compared to the effect of NPY. The feeding effect of central MCH administration is counteracted not only by α-MSH as just mentioned, but also by glucagon-like peptide (GLP-1) and neurotensin. As is the case for NPY, central leptin
administration decreases hypothalamic MCH expression and prevents MCH-induced increase in food intake. However, contrary to what is observed with NPY, long-term central MCH administration fails to produce sustained increases in food intake or in body weight gain, thus obesity. This is in contrast with the observation that, in the obese ob/ob mouse, hypothalamic MCH expression is increased and may participate in the final development of the obese phenotype. To strengthen the physiological role of MCH in food intake regulation, mice carrying a targeted deletion of the MCH gene have been produced. When compared to controls, these mice are hypophagic, leaner, have decreased carcass lipids, and increased metabolic rate. Thus, MCH does represent an important hypothalamic pathway in the regulation of body weight homeostasis, a pathway further completed recently by the discovery of a 353 amino acid G-protein-coupled receptor, to which MCH specifically binds. Such a receptor is present in the hypothalamus and many other brain regions, in keeping with the several functions, beyond the feeding behavior, that are under the influence of MCH.

Effects of Orexins

Orexin A and B (from the Greek word for appetite) have been discovered recently and are also referred to as ‘hypocretins’ (due to their hypothalamic location and sequence analogy to secretin). Orexin A (33 amino acids) and orexin B (28 amino acids) neurons are restricted to the lateral and posterior hypothalamus, whereas both orexin A and orexin B fibers project widely into different areas of the brain\(^\text{(74,75)}\). The corresponding cloned receptors, OX1 and OX2, are found in the hypothalamus (ventromedial hypothalamic nucleus, paraventricular nucleus) a distribution that is receptor-specific. The stimulatory effect of central administration of orexin on food intake is much weaker than that of NPY, and is smaller than that elicited by MCH. Orexin A is more potent than orexin B in eliciting feeding, and its effect is consistent, whereas that of orexin B is not. When given peripherally, orexin A rapidly enters the brain by simple diffusion as it is highly lipophilic, while orexin B with its low lipophilicity is degraded, thus failing to reach the brain adequately. The fact that orexin B is easily inactivated by endopeptidases could be one of the reasons for its relative inefficiency in regulating food intake. In a way similar to what has been observed with NPY, some of the centrally elicited effects of orexin A,
e.g. the stimulation of gastric acid secretion, are mediated by an activation of the parasympathetic nervous system, favoring anabolic processes\(^{(76)}\).

Leptin administration produces a diminution of orexin A levels in the lateral hypothalamus, a finding that is in keeping with the observation of the presence of numerous leptin receptors on orexin-immunoreactive neurons in the lateral hypothalamus\(^{(77)}\). Additional data must be gathered for the physiological role of the orexin system in food intake regulation to be better understood.

### 3.9.4. Effects of Opioids

The endogenous opioid system has long been known to play a role in the regulation of ingestive behavior. The opioid peptides exert their action via a complex receptor subtype system implicating kappa, mu and delta receptors for, respectively, dynorphin, \(\beta\)-endorphin and the enkephalins\(^{(78)}\). The specific modulation of taste and food intake can be partly understood by the use of selective receptor subtype agonists and antagonists. Typically, the central administration of opioid agonists stimulates food intake, decreases the latency to feed, increases the number of interactions with the food, favors fat as well as sucrose ingestion, and increases body weight gain. In contrast, the central administration of opioid antagonists does the reverse, decreasing food intake and body weight\(^{(79)}\). The three major types of opioid receptors, mu, kappa, delta, have been cloned and belong to the G-protein-coupled family. Recently, another receptor highly homologous to the opioid receptors, but one that does not bind any opioid peptide with high affinity, has been cloned. This opioid receptor like (ORL-1) is widely distributed within the central nervous system (CNS), the hypothalamus, hippocampus, and the amygdala, in particular. The endogenous ligand for this opioid-like orphan receptor has now been isolated\(^{(80)}\). It is called nociceptin (as it increases pain responsiveness), or orphanin FQ. It is an 18 amino acid peptide which resembles dynorphin A and has a marked affinity for ORL-1. Nociceptin and ORL-1 thus constitute a new peptidergic system within the CNS, a system of potential interest as it is present not only in rodents, but also in humans. When given centrally, nociceptin stimulates food intake in satiated rats, an effect that is blocked by an opioid antagonist, naloxone. As naloxone does not act at the level of ORL-1, this indicates that stimulation of food intake by nociceptin
involves, at some ill-defined steps, the function of the ‘classical’ opioid system. Microinjection of nociceptin into two brain areas implicated in food intake (the ventromedial hypothalamic nucleus and the nucleus accumbens) also results in increased in food intake\(^{(81)}\). The physiopathological implications of these findings will soon be unraveled.

3.9.5. Opioids and Obesity

The susceptibility to diet-induced obesity in the rat is strain dependent. For example, some strains of rats (e.g. Osborne-Mendel) overeat and become obese when fed a diet rich in fat. Other strains (e.g. S5B/P1) are resistant to high fat diet-induced obesity\(^{(82)}\). In this context, it is interesting that central administration of a kappa opioid receptor antagonist decreases the intake of a high fat diet in the obesity-prone rats, while it does not do so in the obesity-resistant ones. In contrast, the central administration of a kappa opioid receptor agonist increases the intake of a high fat diet in obesity prone rats, while it increases the intake of any type of diet in obesity-resistant animals. It is thus conceivable that the sensitivity to opioids differs from strain to strain, possibly from species to species. It is also possible that, within the brain areas constituting the opioid system, the distribution of the opioids, that of their receptors, may vary from strain to strain. This may lead to a strain-specific opioid dependency of the food intake process and evolution to obesity\(^{(82)}\). The likely importance of the opioid system in obesity is illustrated by the observation that the peripheral administration of compounds with potent opioid antagonistic activity to obese rats results in rapid, marked and sustained decreases in food intake and body weight gain\(^{(83)}\).

3.10. ANOREXIGENIC PEPTIDES

3.10.1. Effects of Cocaine- and Amphetamine-Regulated Transcript (CART)

Cocaine- and amphetamine-regulated transcript (CART) is a recently discovered hypothalamic peptide which is regulated by leptin and is endowed with appetite-suppressing activity. In the rat, the CART gene encodes a peptide of either 129 or 116 amino acid residues\(^{(84)}\). In contrast, only the short form of CART exists in humans. The mature peptide contains several potential cleavage sites and CART may be post-
transcriptionally processed into several biologically active fragments. Thus, in most tissues studied, CART peptides are short, CART being found in the rat hypothalamus. This tissue processing of CART resulting in neuropeptides of different lengths may indicate that different CART peptides have different biological functions. Acute i.c.v. CART administration to normal rats produces a dose-dependent decrease in food intake. CART also transiently decreases the NPY elicited feeding response in normal rats\(^{85}\). Finally, CART appears to have a tonic inhibitory influence on food intake, as treatment of rats with anti-CART antiserum results in increased food intake. CART is regulated, in part, by leptin as chronic peripheral leptin administration to the leptin-deficient ob/ob mice results in a definite augmentation of the low expression of CART measured in the hypothalamic arcuate nucleus of these animals, an increase that is paralleled by the observed decrease in body weight. CART expression is also markedly reduced in the genetically obese leptin-resistant fa/fa rat, thus possibly playing a role in the hyperphagia of this animal. The physiological and pathological importance of CART has yet to be substantiated, although preliminary results with chronic infusion of the neuropeptide appear to indicate that it markedly reduces food intake and body weight of both normal and obese rats.

3.10.2. Effects of Corticotropin-releasing Hormone (CRH)

Apart from its role as controller of the hypothalamo-pituitary-adrenal (HPA) axis, CRH, a 41 amino acid neuropeptide, also functions as a central effector molecule that brings about a state of negative energy balance and weight loss. This is due to the ability of central CRH to decrease food intake\(^{86}\), to increase the activity of the sympathetic nervous system and to stimulate thermogenesis. CRH also influences gastrointestinal functions, inhibiting gastric acid secretion and gastric emptying, processes that are controlled by the parasympathetic nervous system. Chronic i.c.v. CRH administration in normal, genetically obese fa/fa rats, as well as in monkeys, decreases food intake and body weight, partly by acting on energy dissipating mechanisms. Central microinjections of CRH were shown to inhibit NPY-induced feeding, in keeping with the notion that the locally released CRH could restrain the effect of NPY and/or of other orexigenic signals. Leptin administration results in transient increases in hypothalamic CRH levels, thus
potentially favoring the CRH effects just mentioned. The leptin effect on CRH could occur via its increasing CRH type 2 receptor (CRHR-2) expression in the ventromedial hypothalamus, as these receptors are potentially responsible for the CRH-mediated decrease in food intake and sympathetic nervous system activation\(^{87,88}\).

3.10.3. The Melanocortin System and Effects of \(\alpha\)-Melanocyte-stimulating hormone (\(\alpha\)-MSH)

Pro-opiomelanocortin (POMC) is the precursor of many different molecules, the melanocortins, among which are ACTH, \(\beta\)-endorphin, the melanocyte-stimulating hormones (\(\alpha\)-,\(\beta\)-,\(\gamma\)-MSH). The \(\alpha\)-melanocyte-stimulating hormone \(\alpha\)-MSH is a 13amino acid peptide which binds with different affinities to five different subtypes of G-protein coupled receptors. An involvement of \(\alpha\)-MSH in body weight homeostasis via an interaction with the melanocortin-4 (MC4), possibly the MC3 receptors, has been recently described. MC3 receptors are present mainly in the hypothalamus, MC4 receptors throughout the brain and in the sympathetic nervous system\(^{89}\). When administered i.c.v. to normal rats, \(\alpha\)-MSH decreases food intake, as does the central administration of a stable linear analog of \(\alpha\)-MSH, NDP-MSH\(^{90}\). The relationships existing between the melanocortins, their receptor subtypes and feeding have been illustrated by studying synthetic melanocortin receptor agonists and antagonists, amongst which are the compounds called MTII and SHU9119. The i.c.v. administration of the agonist MTII markedly and dose-dependently inhibits food intake, while that of the antagonist SHU9119 markedly and dose-dependently stimulates food intake process. The co-injection of equal concentrations of the agonist and of the antagonist results in a food intake that is identical to that of control rats. In addition, MTII inhibits or suppresses, depending on the dose, the feeding response elicited by neuropeptide Y, in keeping with the observation that both MC3 and MC4 receptors are found in CNS sites in which NPY neurons are also present\(^{91}\).

The effect of \(\alpha\)-MSH in decreasing food intake is under the ‘tonic’ inhibitory influence from a melanocortin-receptor antagonist called ‘agouti-related protein’ (AGRP). When an active fragment of AGRP is administered i.c.v. to rats, an increased food intake is observed. Moreover, when \(\alpha\)-MSH is similarly administered, the observed decrease in
food intake is blocked by the further addition of AGRP\textsuperscript{(92)}. The fundamental importance of the MC4 receptors has been highlighted by obtaining transgenic mice lacking the MC4 receptors (MC4-R-deficient mice). These mice (female and male) exhibit increased food intake and become obese. Both sexes have marked hyperinsulinemia, hyperleptinemia, with either normoglycemia (females) or hyperglycemia (males), plasma corticosterone levels being normal. These data support the view that MC4 receptors are essential in the cascade of events normally leading to decreased food intake and leanness. The decreased food intake produced by α-MSH and the subsequent cascade of events summarized above is accompanied by a change in the activity of the sympathetic nervous system. Thus, activation of the MC3/MC4-receptor system by the agonist MTII administered centrally results in a marked, specific, dose-dependent activation of the sympathetic nerves innervating the brown adipose tissue, as well as the renal and lumbar beds, while no change in blood pressure or heart rate is observed\textsuperscript{(93)}. The combination of decreased food intake and increased sympathetic activation with likely increase in energy dissipation suggests that the melanocortin system is well adapted to play a role in decreases in body weight. Since the main central effects of leptin are to decrease food intake and body weight, and to increase energy dissipation, it has been postulated that this hormone could bring about these changes by influencing the melanocortin system. It is thus of interest to observe that the effect of leptin in decreasing food intake is blocked by a MC4 receptor antagonist (SHU9119), and that pretreatment with the antagonist is able to prevent the effects of leptin in decreasing both food intake and body weight. This effect is specific as the antagonist did not affect the decreased food intake produced by another peptide (GLP-1). Thus, the MC4-receptor signaling is important in mediating the effects of leptin. In keeping with this finding is the observation that the MC4 receptor agonist, MTII, which decreases food intake in normal animals, also suppresses the hyperphagia of the leptin-deficient ob/ob mice. This suggests that leptin acts via MC4 receptors and that in the absence of leptin, i.e. in ob/ob mice, the lack of signaling through MC4 receptors would be responsible for the increased food intake, a viewpoint that remains to be fully validated\textsuperscript{(94)}.

When considering POMC (the precursor of melanocortins, of α-MSH) and AGRP (the antagonist of the MC4 receptor), it is of interest to observe that the lack of leptin in the
ob/ob mouse (or lack of leptin signaling in the db/db one) is accompanied by a decrease in POMC expression and an increase in that of AGRP. Moreover, leptin administration leads to an increase in POMC expression and a decrease in that of AGRP\textsuperscript{(95)}. It may thus be concluded that leptin decreases food intake and body weight, in part by favoring the action of melanocortin neuropeptide(s) at the MC4 receptor, while concomitantly preventing the inhibitory influence of AGRP on this same receptor, a concept excellently reviewed elsewhere. This specific effect of leptin is probably additive to its inhibitory one on hypothalamic NPY levels, NPY being one of the most potent food stimulators as described above, and being co-expressed with AGRP within the arcuate nucleus of the hypothalamus\textsuperscript{(96)}.

3.10.4. The Melanocortin System and Obesity

Obesity, as mentioned above, may result from altered functions of the MC4 receptors. This is illustrated in a global fashion by the observation that when the melanocortin receptor agonist (MTII) is administered i.c.v. to fasted refed hyperphagic mice, to obese ob/ob mice, to yellow (Ay) obese mice, to NPY hyperphagic mice, their respective hyperphagia is largely canceled. In addition, it has been recently demonstrated that mice lacking POMC (hence lacking subsequent α-MSH synthesis and its inhibitory effect on feeding via its binding to MC4 receptors) overeat and become obese, a situation partly reversed by an α-MSH treatment\textsuperscript{(97)}.

The yellow obese mouse is an interesting animal model that underlines the potential importance of the melanocortin system. As reviewed recently, the pigment produced by melanocytes in the skin is under the regulation of α-MSH and a paracrine melanocyte signaling molecule called ‘agouti’ (from American Spanish ‘aguti’, meaning alternation of light and dark bands of colors in the fur of various animals). Agouti binds to MC1 receptors and decreases their signaling, resulting in decreased cAMP levels, thereby inducing melanocytes to synthesize a yellow pigment (pheomelanin). α-MSH binds to MC1 receptors and increases their signaling, resulting in increased cAMP, thereby stimulating the synthesis of a black pigment (eumelanin). The classical agouti hair color of many species appears brown, although the ‘brown’ hairs are in fact black-yellow-black banded hairs, due to the joint effects of agouti and α-MSH. The yellow mouse (Ay)
is heterozygous for a mutation in the agouti gene. This mutation results in an ectopic expression of the agouti protein throughout the body, while the non-mutated gene induces the expression of the agouti protein only in hair follicles. The ectopic expression of agouti is at the origin of many different effects, i.e. yellow hairs, increased linear growth, decreased fertility, obesity. Within the brain, ectopic agouti functions as an antagonist of the MC4 receptor (with little effect on MC3-R), preventing the action of endogenous MC4 receptor agonists, with resulting obesity\(^{98}\). From a physiopathological viewpoint, the agouti protein turns out not to be as esoteric as it may sound. Indeed, a pathway very similar to that of the agouti in the skin has been described in the hypothalamus. Moreover, a novel gene called AGRP (agouti-related protein) or ART (agouti-related transcript) has been discovered in the hypothalamus of rodents as well as humans. It encodes a melanocortin (MC3, MC4) receptor antagonist comprising 132 amino acid residues which, as mentioned above, is the likely natural antagonist of the brain melanocortin system. The importance of the AGRP pathway is supported by the observation that over-expression of human AGRP in transgenic mice induces obesity without producing a yellow color of the fur, AGRP having no effect on MC1 receptors and therefore on the coat color\(^{99}\).

### 3.10.5. Regulation of Appetite

Appetite control implies a control over energy intake. Some researchers argue that it only requires a habitual addition of 20—30 kilocalories per day to lead over a number of years to significant body weight increases which, in turn, leads to an epidemic of obesity. If human beings are the most intelligent life force on this planet, why is it that they cannot adjust their (eating) behavior by the very small amounts which would be required for weight stability rather than weight escalation? Some explanation for this may be found through an examination of the processes involved in the regulation of appetite.

There are clear logical reasons for believing that the expression of appetite—reflected in the pattern of eating and overall energy intake—makes a large contribution to the maintenance of a healthy weight. The impact of appetite on obesity is a time dependent process and will occur at least over many months and usually years. The relationship between appetite and weight gain is therefore part of a developmental, or ageing, process.
and this perspective is important. Appetite fits into an energy balance model of weight regulation but it is not necessary to believe that appetite control is an outcome of the regulation of energy balance. Appetite is separately controlled and is relevant to energy balance since it modulates the energy intake side of the equation. This happens because appetite includes various aspects of eating patterns such as the frequency and size of eating episodes (gorging versus nibbling), choices of high fat or low fat foods, energy density of foods consumed, variety of foods accepted, palatability of the diet and variability in day-to-day intake. All of these features can play a role in encouraging energy intake to exceed energy expenditure thereby creating a positive energy balance. If this persists then it will lead to weight gain.

However, there appears to be no unique pattern of eating or forms of energy intake that will exclusively or invariably lead to an excess of energy intake over expenditure. Nevertheless, some characteristics of the expression of appetite do render individuals vulnerable to over-consumption of food—these characteristics can be regarded as risk factors. These risk factors and other modulating features of the expression of appetite will be disclosed by an analysis of how appetite is regulated.

3.11. CAN APPETITE BE CONTROLLED FOR THE MANAGEMENT OF OBESITY?

It is widely accepted that body weight control and, by implication, a lack of control arises from an interaction between biology and the environment—particularly the food supply reflected in the nutritional environment. The link between the two domains is eating behavior and the associated subjective sensations which make up the expression of appetite. It is this eating behavior which transmits the impact of biological events into the environment, and which also mediates the effects of the nutrient environment on biology. Appetite is not nutrition, rather it is the expression of appetite which allows nutrition to exert an effect on biology, and vice versa. Consequently, adjustments in the processes regulating the expression of appetite should have a significant impact on body weight regulation.
Of course, obesity can be managed by direct changes in the environment itself—to enforce an increase in physical activity or to coercively prevent food consumption. Equally, pharmacological or surgical interventions can be made directly in biology to prevent the assimilation of food or to alter the energy balance. In addition, adjustments in the environment and biology have the potential to influence body weight indirectly by altering food intake—often by acting on the signals involved in processes regulating appetite. The details of these actions will be apparent as the regulation of appetite is examined. Consequently, in principle, appetite can be controlled for the management of obesity. We can envisage interventions either in specific foods which influence biology which in turn adjusts eating behavior or through a direct and deliberate cognitive control of behavior. There are many reasons to believe that an adjustment to the expression of appetite is the best chance we have to prevent the persistent surfeit of energy consumed over energy expended which is currently characterizing much of the world’s population.

It is now accepted that the control of appetite is based on a network of interactions forming part of a psychobiological system. The system can be conceptualized on three levels (Figure 3.4). These are the levels of psychological events (hunger perception, cravings, hedonic sensations) and behavioral operations (meals, snacks, energy and macronutrient intakes); the level of peripheral physiology and metabolic events; and the level of neurotransmitter and metabolic interactions in the brain(100). Appetite reflects the synchronous operation of events and processes in the three levels. When appetite is disrupted as in certain eating disorders, these three levels become desynchronised. Neural events trigger and guide behavior, but each act of behavior involves a response in the peripheral physiological system; in turn, these physiological events are translated into brain neurochemical activity. This brain activity represents the strength of motivation to eat and the willingness to refrain from feeding.

The lower part of the psychobiological system (Figure 3.4) illustrates the appetite cascade which prompts us to consider the events which stimulate eating and which motivate organisms to seek food. It also includes those behavioral actions which actually form the structure of eating, and those processes which follow the termination of eating and which are referred to as post-ingestive or postprandial events.
Even before food touches the mouth, physiological signals are generated by the sight and smell of food. These events constitute the cephalic phase of appetite. Cephalic-phase responses are generated in many parts of the gastrointestinal tract; their function is to anticipate the ingestion of food. During and immediately after eating, afferent information provides the major control over appetite. It has been noted that ‘afferent information from ingested food acting in the mouth provides primarily positive feedback for eating; that from the stomach and small intestine is primarily negative feedback’.

Figure 3.4: Diagram showing the expression of appetite as the relationship between three levels of operations: the behavioral pattern, peripheral physiology and metabolism, and brain activity
3.12. SATIETY SIGNALS AND THE SATIETY CASCADE

Scientifically important components of the appetite system are those physiological events which are triggered as responses to the ingestion of food and which form the inhibitory processes that first of all stop eating and then prevent the re-occurrence of eating until another meal is triggered. These physiological responses are termed satiety signals, and can be represented by the satiety cascade (Figure 3.5). Satiation can be regarded as the complex of processes which brings eating to a halt (cause meal termination) whilst satiety can be regarded as those events which arise from food consumption and which serve to suppress hunger (the urge to eat) and maintain an inhibition over eating for a particular period of time. This characteristic form of an eating pattern (size of meals, snacks etc.) is therefore dependent upon the coordinated effects of satiation and satiety which control the size and frequency of eating episodes.

Initially the brain is informed about the amount of food ingested and its nutrient content via sensory input. The gastrointestinal tract is equipped with specialized chemo- and mechano-receptors that monitor physiological activity and pass information to the brain mainly via the vagus nerve\(^{(102)}\). This afferent information constitutes one class of ‘satiety signals’ and forms part of the pre-absorptive control of appetite. It is usual to identify a post-absorptive phase that arises when nutrients have undergone digestion and have crossed the intestinal wall to enter the circulation. These products, which accurately reflect the food consumed, may be metabolized in the peripheral tissues or organs or may enter the brain directly via the circulation. In either case, these products constitute a further class of metabolic satiety signals. Additionally, products of digestion and agents responsible for their metabolism may reach the brain and bind to specific chemoreceptors, influence neurotransmitter synthesis or alter some aspect of neuronal metabolism. In each case the brain is informed about some aspects of the metabolic state resulting from food consumption.

It seems likely that chemicals released by gastric stimuli or by food processing in the gastrointestinal tract are involved in the control of appetite. Many of these chemicals are peptide neurotransmitters, and many peripherally administered peptides cause changes in food consumption\(^{(103)}\). There is evidence for an endogenous role for cholecystokinin
(CCK), pancreatic glucagon, bombesin and somatostatin. Much recent research has confirmed the status of CCK as a hormone mediating meal termination (satiation) and possibly early phase satiety. This can be demonstrated by administering CCK intravenously (the mouth cannot be used since CCK would be inactivated as soon as it reached the stomach) and measuring changes in food intake and hunger. CCK will reduce meal size and also suppress hunger before the meal; these effects do not depend on the nausea that sometimes accompanies an intravenous infusion\(^{(104)}\). Food consumption (mainly protein and fat) stimulates the release of CCK (from duodenal mucosal cells) which in turn activates CCK-A type receptors in the pyloric region of the stomach. This signal is transmitted via afferent fibres of the vagus nerve to the nucleus tractus solitarius (NTS) in the brainstem. From here the signal is relayed to the hypothalamic region where integration with other signals occurs. The components of this system are set out in Figure 3.6.

Other potential peripheral satiety signals include peptides such as enterostatin, neurotensin and glucagon-like peptide 1 (GLP-1) \(^{(105)}\).

\[\text{Figure 3.5: The satiety cascade illustrating the classes of events which constitute satiety signals arising from food consumption}\]
3.13. SIGNALS FROM ADIPOSE TISSUE:

3.13.1. LEPTIN AND APPETITE CONTROL

One of the classical theories of appetite control has involved the notion of a so-called long-term regulation involving a signal which informs the brain about the state of adipose tissue stores. This idea has given rise to the notion of a lipostatic or ponderstatic mechanism\(^{(106)}\). Indeed this is a specific example of a more general class of peripheral appetite (satiety) signals believed to circulate in the blood reflecting the state of depletion or repletion of energy reserves which directly modulate brain mechanisms. Such substances may include satietin, adipsin, tumour necrosis factor (TNF or cachectin-so named because it is believed to be responsible for cancer induced anorexia) together with other substances belonging to the family of neural active agents called cytokines. In 1994 a landmark scientific event occurred with the discovery and identification of a mouse gene responsible for obesity. A mutation of this gene in the ob/ob mouse produces a phenotype characterized by the behavioral trait of hyperphagia and the morphological
trait of obesity. The gene controls the expression of a protein (the OB protein) by adipose tissue and this protein can be measured in the peripheral circulation. The identification and synthesis of the protein made it possible to evaluate the effects of experimental administration of the protein either peripherally or centrally. Because the OB protein caused a reduction in food intake (as well as an increase in metabolic energy expenditure) it has been termed ‘leptin’. There is some evidence that leptin interacts with NPY, one of the brain’s most potent neurochemicals involved in appetite, and with melanocortin-4 (MC4). Together these and other neuromodulators may be involved in a peripheral—central circuit which links an adipose tissue signal with central appetite mechanisms and metabolic activity (Figure 3.7). In this way the protein called leptin probably acts in a similar manner to insulin which has both central and peripheral actions; for some years it has been proposed that brain insulin represents a body weight signal with the capacity to control appetite.

At the present time the precise relationship between the OB protein and weight regulation has not been determined. However, it is known that in animals and humans which are obese the measured amount of OB protein in the plasma is greater than in lean counterparts. Indeed there is always a very good correlation between the plasma levels of leptin and the degree of bodily fattiness\(^\text{107}\). Therefore although the OB protein is perfectly positioned to serve as a signal from adipose tissue to the brain, high levels of the protein obviously do not prevent obesity or weight gain. However, the OB protein certainly reflects the amount of adipose tissue in the body. Since the specific receptors for the protein (namely OB receptor) have been identified in the brain (together with the gene responsible for its expression) a defect in body weight regulation could reside at the level of the receptor itself rather than with the OB protein. It is now known that a number of other molecules are linked in a chain to transmit the action of leptin in the brain. These molecules are also involved in the control of food intake, and in some cases a mutation in the gene controlling these molecules is known and is associated with the loss of appetite control and obesity. For example, the MC4-R mutation (melanocortin-4 receptor) leads to an excessive appetite and massive obesity in children, just like the leptin deficiency.
Ghrelin

Ghrelin is a peptide released by cells in the fundus of the stomach that stimulates the release of growth hormone from the pituitary and was identified by Kojima et al. in 1999\(^\text{(108)}\). Ghrelin rises before and falls after each ad libitum meal and increases food intake. In humans ghrelin levels peak in the morning (08.00 hours), at noon (12.00 to 13.00 hours) and in the evening (17.00 to 19.00 hours) and fall after each peak. Obese individuals have lower fasting ghrelin levels than lean individuals and reduced suppression of ghrelin secretion after a meal. A fat rich meal has a smaller suppressive effect on plasma ghrelin concentration than a carbohydrate-rich meal regardless of obesity status. So far, no effect of dietary fatty acid profile on total ghrelin levels has been reported.
3.14. SYMPTOMS AND COMPLICATIONS OF OBESITY\(^{(109)}\)

The health risks associated with obesity include:

1. Breathing disorders (e.g., sleep apnea, chronic obstructive pulmonary disease)
2. Certain types of cancers (e.g., prostate and bowel cancer in men, breast and uterine cancer in women)
3. Coronary artery disease (CAD)
4. Depression
5. Diabetes
6. Gallbladder or liver disease
7. Gastroesophageal reflux disease (GERD)
8. Hypertension
9. Dyslipidemia
10. Joint disorders (e.g., osteoarthritis)
11. Stroke

People who are obese may have the symptoms of the medical conditions mentioned above. Hypertension, dyslipidemia, breathing problems, and joint pain (in the knees or lower back) are common. The more obese a person is, the more likely they are to have medical problems related to obesity.

Aside from the medical complications, obesity is also linked to psychosocial problems such as low self-esteem, discrimination, difficulty finding employment, and reduced quality of life.

3.14.1. Diagnosis\(^{(11)}\)

The history, physical examination and laboratory evaluation of overweight and obese patients are directed toward three goals: 1) To identify secondary causes of obesity (Differential diagnosis), 2) To identify comorbid conditions, 3) To establish the patient’s dietary and activity habits.
3.14.2. Diagnosis; History

The history should include questions about diseases for which overweight and obese patients are at higher risk, including hypertension, impaired glucose tolerance or diabetes, hyperlipidemia, heart disease, pulmonary disease and sleep apnea. These conditions may cause minimal or no symptoms and therefore may be present for months or years before a diagnosis is made. Finally, inquiring about past and present dietary and activity habits is important for subsequent discussions of medical and surgical management.

3.14.3. Physical examination and laboratory tests

Height and weight measurements are used to classify patients as overweight or obese according to BMI criteria. However, these criteria may not apply to patients who have gained weight as the result of increased muscle mass from intensive exercise. Evaluation of abnormal obesity requires the use of tape measure. A waist circumference (obtained at the level of the superior iliac crest) greater than 40 inches (102cm) in a man or greater than 35 inches (88cm) in a woman considered abnormal.

Laboratory tests include estimation of lipid profile, blood glucose, thyroid stimulating hormone (all overweight patients should have documentation of normal thyroid function) and liver function tests are done. A fasting lipid profile should be obtained to complete the cardiovascular risk assessment and if necessary treatment should be initiated according to the guidelines from the National Cholesterol Education Program Expert Panel. This panel also incorporated several non lipid risk factors for cardiovascular diseases into its recommendations for clinical care by defining criteria for a condition that has known as the metabolic syndrome also called syndrome X, the deadly quartet and the insulin resistance syndrome.

Although obesity is associated with abnormal levels of a number of hormones and cytokines including leptin, ghrelin, interleukins and tumor necrosis factor; measurement of these variables should be limited to research protocols and are not commonly recommended for general clinical practice.
3.14.4. Differential Diagnosis

It is important for clinicians to be alert for secondary medical causes of obesity but also to be aware that in most cases treatment of these coexisting diseases rarely leads to complete reversal of the obese state. As an example hypothyroidism is relatively common in general population and may be present in an obese patient but the weight loss that might be expected with thyroid hormone is limited and variable.

A number of medications can lead to unwanted weight gain and obesity; if possible, such patients should be switched to alternative agents.

3.15. OBESITY MANAGEMENT\(^{(37)}\)

Many obese persons can achieve short-term weight loss by dieting alone, but successful long-term weight maintenance is much more difficult to achieve. Weight cycling and yo-yo dieting are terms used popularly to describe repetitive cycles of weight loss and subsequent regain. Although some adverse consequences have been associated with weight cycling, available data on the health effects of weight cycling are inconclusive and should not deter obese persons from attempting to lose weight. Currently available weight loss treatments include (1) dietary intervention, (2) increased physical activity, (3) behavior modification, (4) pharmacotherapy, and (5) surgery.

3.15.1. Dietary Intervention

For most obese people, negative energy balance is more readily achieved by decreasing food intake than by increasing physical activity. Therefore, dietary intervention is considered the cornerstone of weight loss therapy. Weight loss diets generally involve modifications of energy content and macronutrient composition. However, the degree of weight loss achieved depends primarily on the energy content, rather than the relative macronutrient composition, of the diet.
3.15.2. Energy Content

Weight loss diets can be classified according to their energy content:

1. Balanced-deficit diets of conventional foods usually contain more than 1500 kcal/day and an appropriate balance of macronutrients.

2. Low-calorie diets (LCDs) contain 800 to 1500 kcal/day and are consumed as liquid formula, nutritional bars, conventional food, or a combination of these items.

3. Very-low-calorie diets (VLCDs) contain less than 800 kcal/day and are generally high in protein (70 to 100 g/day) and low in fat (<15 g/day). Such diets may be consumed as a commercially prepared liquid formula and may include nutritional bars. VLCDs consumed as regular foods (mostly lean meat, fish, or fowl) are known as protein-sparing modified fasts.

According to treatment guidelines issued by the National Institutes of Health (NIH), persons who are overweight (BMI of 25.0 to 29.9 kg/m²) and have two or more cardiovascular disease risk factors and persons with class I obesity (BMI of 30 to 34.9 kg/m²) should decrease their energy intake by approximately 500 kcal/day.

This deficit in energy intake generally promotes weight loss of 1 pound (0.45 kg) per week and results in about a 10% reduction of initial weight at 6 months. The NIH guidelines recommend a more aggressive energy deficit of 500 to 1000 kcal/day for persons with more severe obesity (BMI of 35.0 kg/m² or higher). In such individuals, this energy deficit generally produces weight loss of 1 to 2 pounds/week and results in a 10% weight loss at 6 months.

Total daily energy requirements can be estimated by using standard equations (e.g., the Harris-Benedict equation(111) or the World Health Organization equation(112)), which are based on the patient's size, age, gender, and activity level. However, the use of standard equations is cumbersome and may be unreliable in obese persons. Use of the simple dietary guidelines outlined in Table 3.6 is suggested as an alternative to a specific energy deficit diet based on the individual's daily energy requirements. Patients who follow these guidelines generally lose weight. Because many patients do not fully adhere to their
prescribed diet, the energy content of the diet should be regularly adjusted according to the patient’s weight loss response.

More than 30 prospective randomized clinical trials have investigated the effectiveness of LCDs for weight loss\(^{(110)}\). The composite results of these trials indicate that an LCD providing 1000 to 1500 kcal/day induces about an 8% weight loss after 16 to 26 weeks of treatment. However, these results may not be typical of the results obtained when an LCD is prescribed in routine clinical practice because trial participants volunteered to enroll in a weight loss study and most study protocols included some form of behavior modification therapy.

The use of VLCDs induced a weight loss of about 15% to 20% in 12 to 16 weeks of treatment, but this weight loss was not usually maintained. In fact, several randomized trials have shown that weight regain is greater after VLCD than LCD therapy. Therefore, 1 year after treatment, weight loss with a VLCD is often similar to that obtained with an LCD. In addition, initial weight losses with a VLCD and an LCD are similar when the diets are consumed in the same manner.

For example, the weight loss observed in patients given a liquid diet providing 420 kcal/day was not significantly greater than that observed in persons who consumed a liquid diet providing 800 kcal/day. This finding suggests that patients treated with VLCDs are either less compliant with the diet or sustain a greater decline in energy expenditure than those treated with LCDs. With VLCDs, there is a greater risk of the medical complications associated with dieting, such as hypokalemia, dehydration, and gallstone formation. Patients treated with a VLCD therefore require closer medical supervision than those treated with an LCD.
Table 3.6: Suggested energy and Macronutrient Composition of initial Reduced-Calorie Diet\(^{(112)}\)

<table>
<thead>
<tr>
<th>Body Weight (lb)</th>
<th>Suggested Energy Intake (kcal/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>1000</td>
</tr>
<tr>
<td>200</td>
<td>1200</td>
</tr>
<tr>
<td>250</td>
<td>1500</td>
</tr>
<tr>
<td>300</td>
<td>1800</td>
</tr>
<tr>
<td>350</td>
<td>2000</td>
</tr>
</tbody>
</table>

### 3.15.3. Macronutrient Composition

Altering the macronutrient composition of the diet does not induce weight loss unless total energy intake is reduced. Low fat diets have traditionally been prescribed for weight loss because such diets facilitate energy restriction. Triglycerides, the principal component of dietary fat, increase the palatability and energy density of food. The results of epidemiologic and diet intervention studies suggest that increased dietary fat intake is associated with increases in total energy intake and body weight. Conversely, data from a large number of studies suggest that decreasing fat intake is associated with spontaneous decreases in total energy intake and body weight even when carbohydrate and protein intakes are not restricted.

A direct relationship between changes in dietary fat intake and body weight was found in a meta-analysis of 37 intervention studies involving the Step I or Step II low-fat (<30% kcal as fat) diet recommended by the National Cholesterol Education Program to lower cardiovascular risk. Data from another meta-analysis suggest that the amount of weight loss induced by a low-fat diet is directly related to the severity of obesity.

### 3.15.4. Physical Activity

Although there is a profound increase in energy expenditure during an actual episode of exercise, the addition of regular exercise to a weight loss program has negligible effects on resting energy expenditure (REE). In a meta-analysis of prospective controlled trials
in which obese subjects were randomly assigned to treatment with diet alone or diet plus exercise, the addition of exercise did circumvent the expected decline in REE when REE was adjusted for body mass.

### 3.15.5. Body Composition

The composition of weight loss can be influenced by the addition of exercise to a diet program. Pooled data from two meta-analyses indicated that exercise can reduce the loss of fat free mass (FFM) that occurs with weight loss. When diet-induced weight loss was about 10 kg, regular exercise of low or moderate intensity reduced the percentage of weight lost as FFM from approximately 25% to 12%. Although the difference in weight lost as FFM was large on a percentage basis, it nonetheless represented only a small (1 kg) difference in the absolute amount of FFM lost. This preservation of FFM with exercise may not necessarily reflect preservation of muscle protein but may instead involve increased retention of body water and muscle glycogen. Indeed, nitrogen balance studies have not been able to detect any nitrogen-sparing effect of exercise during diet-induced weight loss in women. Whether there is a difference between the effects of endurance and resistance exercise on FFM conservation is not clear because the available data are limited and conflicting.

### 3.15.6. Diabetes and Coronary Heart Disease

Endurance exercise increased insulin sensitivity and was associated with a decreased risk of development of diabetes and death from cardiovascular disease.

### 3.15.7. Weight Loss

Increasing physical activity alone is not an effective strategy for promoting initial weight loss. Most studies have shown that moderate endurance exercise, such as brisk walking for 45 to 60 minutes, four times a week, for up to 1 year, usually induces only minor weight loss. In obese persons, the energy deficit created by exercise is usually much less and requires more effort than the energy deficit created by a reduced-calorie diet. For example, to lose 1 pound of fat, an obese patient would have to walk or run approximately 4.5 miles/day for 1 week or to consume a 500 kcal/day deficit diet for 1
week. Although exercise is not an effective strategy for inducing initial weight loss, increasing physical activity is an important component of successful long-term weight management. Several large-scale, cross-sectional case studies have shown that obese subjects who were successful in maintaining weight loss for 1 year or more engaged in regular exercise. In several prospective randomized studies, subjects treated with diet plus exercise who continued to exercise sustained significantly larger long-term weight losses than subjects who stopped exercising or subjects treated with diet alone. However, when data were analyzed on an intention-to-treat basis, most prospective randomized trials did not find that exercise had a statistically significant effect on the long-term maintenance of weight loss, presumably because adherence to the exercise program was often poor.

It has been reported that obese patients need to expend approximately 2500 kcal/week to maintain weight loss. This level of energy expenditure can be accomplished through vigorous activity (aerobics, cycling, or jogging) for approximately 30 minutes/day or more moderate activity (brisk walking) for 60 to 75 minutes/day. Most obese persons cannot easily achieve this level of activity. Therefore, prescribed activity goals should be initially modest and increased gradually over time.

3.16. PHARMACOTHERAPY\(^{(37)}\)

3.16.1. Overview

Conventional obesity therapy is associated with a high rate of recidivism. Therefore, the most important goal of pharmacotherapy 1632 is to maintain long-term weight loss. Pharmacotherapy should not be considered a short-term approach for weight loss because patients who lose weight with drug therapy usually regain weight when the therapy is discontinued. Some obese patients do not respond to drug therapy, and long-term success is unlikely if weight loss does not occur within the first 4 weeks of drug treatment.

Moreover, weight loss usually levels off by 6 months of treatment and weight begins to increase after 1 year. This observation implies that the efficacy of weight loss medications declines with time or obesity is a progressive disease, or both.
Treatment outcomes are less successful when pharmacotherapy is administered alone than when it is administered as part of a comprehensive weight loss program that includes diet, exercise, and behavior modification\(^{(113)}\). The use of obesity pharmacotherapy alone exposes patients to the full risks of the drug without the full medical benefits of more comprehensive treatment.

Table 3.7 lists the drugs currently approved by the United States Food and Drug Administration for the treatment of obesity. All such approved weight loss drugs act as anorexiants, with the exception of orlistat, which inhibits the absorption of dietary fat. Three anorexiant drugs have been withdrawn from the market because of the increased incidence of either valvular heart disease (fenfluramine and dexfenfluramine) or hemorrhagic stroke (phenylpropanolamine) associated with their use.

All anorexiant drugs, except mazindol, are derived from phenylethylamine, the amphetamine precursor. The structures of these drugs have been chemically altered to reduce the potential for abuse. Anorexiant medications affect the monoamine (norepinephrine, serotonin, and dopamine) system in the hypothalamus and thereby enhance satiation (level of fullness during consumption of a meal, which influences the amount of food consumed), satiety (level of hunger after consumption of a meal, which influences the frequency of eating), or both. Monoamine neurotransmitters are synthesized from tyrosine and stored in granules that release their contents from presynaptic nerve terminals into the interneuronal cleft between presynaptic and postsynaptic nerves.

Table 3.7: Drugs Approved by the United States Food and Drug Administration for the Treatment of Obesity\(^{(54)}\)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<tbody>
<tr>
<td>Benzphetamine hydrochloride</td>
<td>Didrex</td>
</tr>
<tr>
<td>Phenmetrazine tartrate</td>
<td>Bontril, Plegine, Prelu-2</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Ionamin, Adipex-P, Fastin</td>
</tr>
<tr>
<td>Diethylpropion hydrochloride</td>
<td>Tenuate, Tenuate Dospan</td>
</tr>
<tr>
<td>Mazindol</td>
<td>Sanorex, Mazanor</td>
</tr>
<tr>
<td>Sibutramine hydrochloride</td>
<td>Meridia</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Xenical</td>
</tr>
</tbody>
</table>
Only a small portion of the monoamines released into the interneuronal cleft actually bind to postsynaptic receptors and thus transmit a signal from one nerve to the other. Most of the released monoamines are taken back up into the presynaptic nerve terminal, where they are either degraded or repackaged into granules for future release.

Weight loss pharmacotherapy is approved for patients with no contraindications to therapy who have BMI greater than 30 kg/m² or a BMI between 27 and 29.9 kg/m² and an obesity-related medical condition.

3.16.2. Agents approved for long term use

**Sibutramine**

Sibutramine inhibits the neuronal reuptake of norepinephrine, serotonin, and, to a lesser degree, dopamine. It enhances satiation rather than satiety. In humans, sibutramine also appears to promote a small increase in metabolic rate several hours after its administration. The currently recommended initial dose of sibutramine is 10 mg/day. This daily dose can be decreased or increased by 5 mg if tolerance is poor or weight loss is inadequate. Administration of sibutramine at doses between 1 and 30 mg/day for 24 weeks resulted in a dose-dependent weight loss; the weight loss ranged from 0.9% of initial body weight with placebo to 7.7% with sibutramine at 30 mg/day. Results from two 1-year, randomized, controlled trials of the effectiveness of sibutramine treatment in producing and maintaining weight loss have been reported. The results of one trial have appeared only in abstract form, and the other trial involved only obese subjects with medication-controlled hypertension. In both trials, all participants received minimal adjunctive weight management therapy and the placebo group lost less weight than usually observed in placebo groups from other trials. Subjects treated with sibutramine (10 to 20 mg/day) lost more weight than those treated with placebo. In the first study, 39% of patients randomly assigned to sibutramine therapy lost 10% or more of their initial body weight compared with 9% of those randomly assigned to receive placebo. In the second study of hypertensive obese patients, 13% of patients who received sibutramine therapy lost 10% or more of their body weight compared with 4% of those who received placebo.
Results have also been reported from two prospective, randomized, controlled trials that evaluated the efficacy of sibutramine therapy in long-term weight management after a predetermined amount of weight was lost. In the first trial, obese subjects who lost at least 6 kg after a 4-week VLCD resumed a regular diet with diet counseling and were randomly assigned to 1 year of treatment with placebo or sibutramine. In the year after randomization, sibutramine-treated subjects lost an additional 5.2 kg while placebo-treated subjects gained 0.5 kg. Total weight losses in the study were 12.9 kg in sibutramine-treated subjects and 6.9 kg in subjects treated with placebo. The initial weight loss achieved with the VLCD was maintained or increased in 74% of sibutramine-treated subjects compared with only 41% of placebo-treated subjects.

In the second trial, obese subjects who lost more than 5% of their initial weight after 6 months of treatment with sibutramine (10 mg/day) and a 600 kcal/day deficit diet were randomly assigned to treatment with either sibutramine (increased to 15 or 20 mg/day) or placebo. All subjects received dietary counseling. Nearly half of the subjects who entered the study failed to complete the 18-month treatment program. Among subjects who completed the study, 43% of those treated with sibutramine but only 16% of those treated with placebo maintained 80% or more of their original 6-month weight loss. On average, subjects who continued sibutramine maintained their weight loss for 1 year and then experienced a slight and progressive increase in weight; subjects who were switched to placebo experienced a progressive increase in weight as soon as sibutramine therapy was stopped.

The most common side effects of sibutramine therapy are dry mouth, headache, constipation, and insomnia. Sibutramine also causes small increases in blood pressure (2 to 4 mm Hg) and heart rate (4 to 6 beats/min). However, some patients experience much larger increases in blood pressure or heart rate and require dose reduction or discontinuation of therapy.

**Orlistat**

Orlistat is synthesized from lipstatin, a product of *Streptomyces toxytricini* mold, which inhibits most mammalian lipases. Orlistat binds to lipases in the gastrointestinal tract and
thereby blocks the digestion of dietary triglycerides. This inhibition of fat digestion reduces micelle formation and, subsequently, the absorption of long-chain fatty acids, cholesterol, and certain fat-soluble vitamins. The degree of fat malabsorption is directly related in a curvilinear fashion to the dose of orlistat administered\(^{(114)}\). Excretion of about 30% of ingested triglycerides, which is near the maximum plateau value, occurs at a dose of 360 mg/day (120 mg three times a day with meals). Orlistat has no effect on systemic lipases because less than 1% of the administered dose is absorbed.

Many clinical trials of orlistat included treatment with low doses (30 and 60 mg three times a day) that were not effective. Therefore, only data obtained with the standard recommended dose of 120 mg three times a day are reviewed here. The effectiveness of orlistat therapy (120 mg three times a day) in promoting and maintaining weight loss has been evaluated in several prospective randomized, controlled trials more than 1 year in duration. At 1 year, about one-third more patients treated with orlistat than treated with placebo lost 5% or more of initial body weight; about twice as many patients treated with orlistat than treated with placebo lost 10% or more of initial weight. Subjects who were enrolled in a trial conducted within a primary care practice setting, which did not include behavior therapy or interaction with a dietitian, did not do as well as those enrolled in trials that provided formal behavior modification and dietary counseling. Successful weight loss was also more difficult to achieve in patients with type 2 diabetes mellitus.

The long-term efficacy of orlistat in maintaining initial weight loss after 1 year has been evaluated in several randomized, controlled trials, including second-year extensions of the 1-year trials just discussed. During the second year of these trials, more liberal energy intake was allowed with a goal of preventing weight regain rather than promoting additional weight loss. About half of the initially randomly assigned subjects completed the second year. After 1 year, both placebo-treated and orlistat-treated groups in all trials regained weight. However, at the end of 2 years, relative weight loss was greater with orlistat than with placebo treatment.

The results of several randomized clinical trials suggest that orlistat administration is associated with a reduction of serum cholesterol concentrations that is independent of the effect of weight loss alone. Even after adjusting for percent weight loss, these studies
found that subjects treated with orlistat sustained a greater reduction in serum LDL-cholesterol concentrations than those treated with placebo. The mechanism responsible for this effect may be related to orlistat-induced inhibition of dietary cholesterol absorption.

The most common side effects associated with orlistat therapy are gastrointestinal complaints. Approximately 70% to 80% of subjects treated with orlistat experienced one or more gastrointestinal events, compared with approximately 50% to 60% of those treated with placebo. These gastrointestinal events were induced by fat malabsorption, usually occurred within the first 4 weeks of treatment, and were of mild or moderate intensity. Subjects rarely reported more than two episodes despite continued orlistat treatment. Orlistat treatment can also affect fat-soluble vitamin status and the absorption of some lipophilic medications. Therefore, it is recommended that all patients treated with orlistat also receive a daily multivitamin supplement and that orlistat not be taken for at least 2 hours before or after the ingestion of vitamin supplements or lipophilic drugs.

Lorcaserin

Lorcaserin is a serotonin 2C receptor agonist and is thought to aid weight loss by reducing appetite and promoting satiety. The FDA approved lorcaserin in 2012, although it initially denied approval because of concerns that the potential risks of the drug outweighed the benefits. Nonselective serotonergic agonists, such as fenfluramine and dexfenfluramine, carry an increased risk of serotonin-associated cardiac valvular disease. Theoretically, lorcaserin should not have the same cardiac effects because it is a selective agonist of serotonin receptor 2C. However, there are currently few long-term safety data\(^\text{115,116}\).

Lorcaserin appears to have comparable effectiveness to orlistat but to be slightly less effective than phentermine-topiramate\(^\text{115,116}\). Lorcaserin’s safety and effectiveness were evaluated in three randomized, placebo-controlled, double-blind studies that were the basis for FDA approval. These trials included more than 6,000 patients and lasted at least one year. The average weight loss with lorcaserin ranged from 3% to 3.7% over placebo.
In the two trials that excluded patients with diabetes, approximately 47% of participants lost at least 5% of their body weight, compared with 23% for placebo\(^{(117,118)}\).

Lorcaserin appears to have fewer adverse effects than orlistat, although long-term data are limited. The most common adverse effects with lorcaserin include headache, dizziness, fatigue, nausea, dry mouth, and constipation\(^{(117)}\).

Like orlistat, lorcaserin is indicated for obese patients with at least one weight-related comorbidity such as diabetes, hypertension, or dyslipidemia. Response to lorcaserin should be assessed at 12 weeks, and the medication should be discontinued if patients do not lose 5% of their body weight. Although lorcaserin was approved in 2012, as of now, it was not yet available pending a decision to designate lorcaserin as a Schedule IV controlled substance\(^{(119)}\). When it is available, lorcaserin is expected to cost approximately $120 per month\(^{(120)}\).

**Phentermine-Topiramate ER**

Phentermine-Topiramate ER The combination of phentermine and topiramate extended-release is another recent addition to the approved medical options for chronic weight management. Phentermine is an appetite suppressant and topiramate is an anticonvulsant thought to act as an appetite suppressant. Like lorcaserin, phentermine-topiramate was not approved by the FDA when it was first submitted. Concerns were raised about potentially serious adverse effects, such as increased heart rate, depression, suicidal ideation, and cognitive impairment. Phentermine-topiramate ER was evaluated for safety and effectiveness in two large randomized, double-blind, placebo-controlled trials. These trials included 3,700 patients treated for up to one year. The average weight loss in patients taking phentermine-topiramate ER ranged from 6.7% (lowest dose) to 8.9% (recommended dose) over placebo. Sixty-two percent of patients taking the lowest dose and 70% taking the recommended dose lost at least 5% of their body weight, compared with 20% of patients receiving placebo\(^{(118,121)}\).

Phentermine-topiramate ER appears to be slightly more effective than orlistat and lorcaserin. However, concerns about phentermine-topiramate ER’s effect on heart rate limit its use in patients with cardiovascular disease\(^{(115)}\). The most common adverse effects
Evaluation of *Caralluma fimbriata* extract in animal models of obesity

with phentermine-topiramate ER include paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth\(^{(122)}\).

After 12 weeks, if a patient has not lost at least 3\% of baseline body weight, phentermine-topiramate ER may be discontinued, or the dosage may be increased. In the latter case, weight loss should be reevaluated after an additional 12 weeks. If 5\% weight loss has not been achieved at that point, the drug should be discontinued. Phentermine-topiramate ER should be discontinued gradually because abrupt cessation of topiramate has been associated with seizures in some patients\(^{(121,122)}\). Combination phentermine-topiramate is estimated to cost approximately $180 per month\(^{(120)}\). Any agent that contains phentermine is designated as a Schedule IV controlled substance.

In 2012 the U.S. Food and Drug Administration approved phentermine-topiramate ER as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of: ≥30 kg/m\(^2\) or ≥27 kg/m\(^2\) (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia.

3.16.3. Sympathomimetics (Approved for short term use)

Four sympathomimetic agents are currently approved for short-term use as weight-loss adjuncts: phentermine, diethylpropion, benzphetamine, and phendimetrazine. Phentermine and diethylpropion are Schedule IV drugs, while benzphetamine and phendimetrazine are Schedule III drugs. Sympathomimetic agents demonstrate a modest weight-loss benefit by causing early satiety. However, evidence is lacking about the long-term risks and benefits of these medications. These agents are contraindicated in patients with coronary heart disease, hypertension, hyperthyroidism, and in patients with a history of drug abuse. For these reasons, primary care physicians may choose to avoid prescribing them in favor of other agents\(^{(115)}\).

3.16.4. Other Medication Options

An alternative prescribing approach for obese patients with comorbidities is to take a weight centric approach to overall disease management. In other words, whenever
possible, the physician should select medications that treat the comorbid condition and that also lead to weight loss or are at least weight-neutral. For example, metformin may be an appropriate choice for obese patients with type 2 diabetes because it is not associated with weight gain (as opposed to insulin, for example) and may result in weight loss in some patients\(^\text{115}\).

### 3.16.5. Withdrawn pharmacotherapy

Many anti-obesity medications, like drugs in most fields of pharmacotherapy, have been withdrawn after licensing because of safety concerns and adverse events that outweigh the modest benefits of treatment (Table 3.8\(^\text{123}\)).

Two anti-obesity drugs have been approved by NICE but subsequently withdrawn: Rimonabant in 2009 and Sibutramine in 2010\(^\text{124}\).

**Table 3.8: Initially approved pharmacotherapy and their current status\(^\text{123}\)**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTRODUCED</th>
<th>MECHANISMOFACTION</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinitrophenol</td>
<td>1930s</td>
<td>Increases metabolic rate</td>
<td>Withdrawn—risk of neuropathy and cataracts</td>
</tr>
<tr>
<td>Amphetamines: dexamphetamine, methamphetamine</td>
<td>1936</td>
<td>Appetite suppression</td>
<td>Banned, restricted or discouraged—dependency and abuse potential, cardiovascular adverse effects</td>
</tr>
<tr>
<td>Aminorex</td>
<td>1965</td>
<td>Appetite suppression</td>
<td>Withdrawn1968—pulmonary hypertension</td>
</tr>
<tr>
<td>Mazindol</td>
<td>1970s</td>
<td>Appetite suppression</td>
<td>Discontinued1993—Australia</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>1963–</td>
<td>Appetite suppression</td>
<td>Withdrawn1997—valvular heart disease, pulmonary Hypertension</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>1985–</td>
<td>Appetite suppression</td>
<td>Withdrawn1997—valvular heart disease, pulmonary Hypertension</td>
</tr>
<tr>
<td>Orlistat</td>
<td>1998–</td>
<td>Decreased fat absorption</td>
<td>Also available over-the-counter in several countries</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>2006–Europe</td>
<td></td>
<td>Withdrawn2009—potential of serious psychiatric disorders</td>
</tr>
</tbody>
</table>
3.17. Surgical Therapy

3.17.1. Overview

Gastrointestinal surgery is the most effective approach for inducing major weight loss in extremely obese patients. In 1991, guidelines for the surgical treatment of obesity were established by an NIH consensus conference\(^{(125)}\). According to these guidelines, eligible candidates for surgery include patients with a BMI of 40 kg/m\(^2\) or higher or those with a BMI of 35.0 to 39.9 kg/m\(^2\) and one or more severe medical complications of obesity (e.g., hypertension, heart failure, type 2 diabetes mellitus, or sleep apnea). Additional eligibility criteria are inability to maintain weight loss with conventional therapy, acceptable operative risks, absence of active substance abuse, and the ability to comply with the long-term treatment and follow-up required.

Current surgical procedures for obesity can be categorized as those that primarily cause gastric restriction and those that primarily cause nutrient maldigestion and malabsorption. All procedures have been performed laparoscopically, but the laparoscopic approach is technically challenging and usually requires more operating room time.

3.17.2. Bariatric Surgery

Multiple studies have demonstrated that bariatric surgery produces substantial and sustained weight loss, and results in amelioration of obesity-related comorbidities, compared with usual care. Bariatric surgery also appears to improve long-term survival. Perhaps just as important, bariatric surgery has the potential to dramatically improve a patient’s quality of life\(^{(126)}\).

Bariatric surgery may be considered in adults who have not achieved weight loss with dietary or other treatments and who have a BMI of 40 kg/m\(^2\) or greater, or for those who have a BMI of 35 kg/m\(^2\) or greater with significant obesity-related comorbidities (e.g., severe hypertension, type 2 diabetes, obstructive sleep apnea).\(^{(75)}\) Bariatric surgery may also benefit patients with obesity-related comorbidities who have a BMI of 35 kg/m\(^2\) or lower, but it is not routinely recommended for these patients\(^{(127)}\).
According to the World Health Organisation (WHO), weight management accounts for tens of billions of dollars in direct healthcare costs throughout the world. A panel of experts convened by WHO stated on 12 June 1997 that its impact is so diverse and extreme that it should now be regarded as one of the greatest neglected public health problems of our time. It has an impact on health, which may well prove to be as great as that of smoking’ (World Health Organisation, 1997).

3.17.3. Supplemental approaches to weight management

There are several treatises on Ayurveda which are used even today in modern practice. Ayurveda and other systems of traditional medicine use modern methods of documentation and data preservation. Even so, traditional texts are believed to describe not more than 5,000 plants of medicinal value.

Many medicinal plants and vegetables of medicinal value used across India are not documented in the texts but are used nevertheless on a daily basis for various curative properties by native populations in India.

It is noteworthy that in native Indian populations, many ailments that afflict developed societies are unheard of. For example, type 2 diabetes is uncommon amongst tribals in India. The same is the case with hypertension, hypercholesterolemia and obesity.

In urban India, the incidence of type 2 diabetes, obesity and related ailments is on the rise, whereas rural Indian populations are largely unaffected by this rise.

In addition to their healthy lifestyles, Indian native populations employ a wide range of dietary supplements which form part of their regular traditional diets.

Many herbs are used as supplements. Some in fact are used as vegetables and condiments and cooked along with daily food.

A typical example would be fenugreek (*Trigonella foenum-graecum*). Indian cooking as a condiment, flavor enhancer and digestive. Fenugreek is used in Roasted fenugreek seeds are used as a condiment, fenugreek leaves are used as vegetables and raw fenugreek seeds are given as digestives. Fenugreek has been well documented in Indian texts for its
use as an anti-diabetic agent, which has been confirmed by modern-day clinical studies. Fenugreek has also been demonstrated to reduce LDL levels in blood, in controlled double-blind clinical trials.

Another example is bitter gourd or karela (*Momordia charantia*). Bitter gourd is used as a vegetable in Indian cooking. The bier principles found in *momordia* are known to be useful in the management of elevated blood sugar. Diabetics in India are prescribed *momordia* as part of their daily diet, even by allopathic practitioners.

There are innumerable such examples of functional foods being used in Indian cuisine. The traditional Indian approach to health has always been holistic in nature, incorporating a healthy lifestyle, stress management, functional foods and prescribed herbal remedies for specific ailments.

Tribal Indians use the same approach in health management. Use of locally available resources is central to this concept.

Accordingly, their daily diet reflects this approach, in that plants of medicinal value are treated as, and consumed as, vegetables.

In keeping with the holistic approach, native populations of India consume several locally growing medicinal plants as part of their diets.

Edible, succulent cactii grow wild all over India and are part of the daily diets of several native populations. The *Caralluma* genus is one such genus of edible cacti, which includes several species, many of which grow across India.

*Caralluma fimbriata* is the most prevalent of these species and it flourishes in large parts of interior India. It grows wild in urban centers as well and is planted as a roadside shrub and as a boundary marker in gardens.

*Caralluma fimbriata* is essentially a vegetable of daily use in tribal India. It is eaten in several forms. It is cooked as a regular vegetable, with spices and salt, it is used in preserves like chutneys and pickles and it is even eaten raw.
3.18. **CARALLUMAFIMBRIATA**\(^{\text{128}}\)

3.18.1. Botanical Description:

*Caralluma fimbriata*, also known as *Caralluma ascendens*, belongs to the family ASCLEPIADACEAE.

Local Names:

Kullee mooliyan, kallimudayan (tamil)

Karallamu (Telegu)

Yugmaphallottatna (Sanskrit)

Ranshabar, makad shenguli, shindala makadi (marathi)

There are other species of *Caralluma* that grow in India. Among these are: *C. indica*, *C. attenuatu*, *C. umbellata*, and *C. stalugmifera*. All these varieties of *Caralluma* are botanically and phytochemically similar to *C. fimbriata* and regularly consumed by the native population across India.
3.18.2. Background of Caralluma Species

*Caralluma fimbriata* is a tender succulent that is found in the wilds of Africa, the Canary Islands, Arabia, southern Europe, Ceylon, and Afghanistan. The *Caralluma* genus of cacti is included among those listed as edible, because the daily diets of numerous natives of India over many centuries include this edible, wild, succulent cacti. Daily consumption is largely due to the fact that the *Caralluma* genus grows ubiquitously in that area.

3.18.3. History of Use

*Caralluma fimbriata* has been in use since centuries in India.

In Western India, *Caralluma fimbriata* is well known as a famine food, appetite suppressant and thirst quencher. The green follicles are eaten, boiled and salted. In Kerala, South India, *Caralluma fimbriata* is used as a vegetable and appetite suppressant among tribal populations. It also finds use today as an appetite suppressant and famine food during times of famine, in the semi-arid regions of India.

*Caralluma fimbriata* is the most prevalent of the genus, as it grows wild in urban centers, is planted as a roadside shrub, and is commonly used as a boundary-marker in gardens. This so-called vegetable is eaten daily in several different forms – cooked as a regular vegetable, placed in preserve like chutneys and pickles, and sometimes eaten raw. To give specific examples, (1) *Caralluma fimbriata* is consumed daily as a vegetable in the Kolli Hills of South India; (2) it is used in pickles and chutney in the arid regions of Andhra Pradesh; and (3) in Western India, *Caralluma fimbriata* is accepted as a famine food – suppressing appetite and quenching thirst. Legend has it that hunting tribes chewed chunks of the *Caralluma* cactus to suppress hunger and thirst when on a long hunt. Most importantly to determine safety, there are no adverse event reports on the Indian subcontinent over the centuries of use. *Caralluma fimbriata* is listed as a vegetable in The Wealth of India, the Indian Health Ministry’s comprehensive compilation on medicinal plants. Key phytochemical ingredients include pregnane glycosides, flavone glycosides, megastigmane glycosides, bitter principles, saponins, various flavonoids, etc.\(^{129}\).
3.18.4. Safety profile

During its entire history of use, over centuries, on the Indian subcontinent, not a single adverse event has been reported on *Caralluma fimbriata*.

**Proposed Mechanisms of Action for Weight Reduction and Safety**

It is postulated that the pregnane glycosides and perhaps other constituents in *Caralluma fimbriata* prevent fat accumulation via blocking citrate lyase. This would be similar to the mechanisms proposed for another product from India, *Garcinia cambogia*\(^{130}\). This is important for two reasons. The mechanism of action of *Garcinia cambogia* has proven to be safe for those desiring to lose weight. In addition, clues as to how *Caralluma fimbriata* works to reduce weight may emanate from our knowledge of *Garcinia cambogia*. The active component in *Garcinia cambogia* is hydroxycitrate (HCA), and HCA has been reported to cause weight loss in humans without stimulating the central nervous system\(^{131}\). Because it is a competitive inhibitor of ATP-citrate lyase, an extra mitochondrial enzyme involved in the initial steps of *de novo* lipogenesis. Consequently, HCA reduces the transformation of citrate into acetyl coenzyme A, a step necessary for the formation of fatty acids in the liver. In addition to its effect of citrate lyase, the postulated blocking of malonyl Coenzyme A by *Caralluma fimbriata* could further lead to a decrease in fat formation in the metabolic pathway. Again similar to *Garcinia cambogia*, *Caralluma fimbriata* is reported to suppress appetite hypothesized to be secondary to effects on the appetite control center of the brain. HCA has been demonstrated to reduce food intake in animals suggesting its role in the treatment of obesity and has been demonstrated to increase the availability of serotonin in isolated rat brain cortex that could affect satiety\(^{132}\). More specifically, it is believed that the pregnane glycosides in *Caralluma fimbriata* inhibit the hunger sensory mechanisms of the hypothalamus (Figure 3.8).
Figure 3.8: Proposed mechanism of action of Caralluma fimbriata

3.18.5. Other Actions of Caralluma

In folklore medicine, plants of the Caralluma species have been used to treat diabetes. In a study using streptozotocin diabetic mice, acute or subacute treatment with C. Arabica caused a statistically significant lowering of circulating blood glucose levels\(^{(133)}\). Streptozotocin-induced diabetes is a model for Type I diabetes mellitus. Accordingly, in these insulin deficient mice, the Caralluma species was able to lower blood glucose suggesting an “insulin-like” action, an increase in insulin release, and/or an ability to sensitize the animal to lesser amounts of insulin. However, one oddity was that in this particular study the glucose tolerance to a glucose challenge appeared better in the control animals even though baseline sugars were higher in control. Similar to C. arabica, extracts from C. attenuata were found to be antihyperglycemic in alloxan-diabetic rats\(^{(134)}\). Animal studies suggest that C. arabica extract is anti-nociceptive and anti-inflammatory\(^{(135,136)}\). Using the hot plate and writhing methods in albino mice and the tail-flick method in Wistar rats, the nociceptive properties of C. arabica were shown. This occurred when the extract was placed on the skin indicating transdermal absorption. The lesser accumulation of edema in the in paws injected with carrageenan indicated anti-inflammatory properties as well. This property was localized to a specific pregnane glycosides.
glycoside from *C. umbellate*\(^{(137)}\). *C. arabica* also has been shown to possess anti-gastric ulcer and cytoprotective properties against damage produced by phenybutazone, indomethacin, ethanol, sodium hydroxide, and/or cold restraint stress\(^{(138)}\). The protective effect was postulated to be via multi mechanisms, including increased gastric production of prostaglandins and mucin and reduced gastric acidity.

3.19. EXPERIMENTAL MODELS TO INDUCE OBESITY IN RATS\(^{(12)}\)

3.19.1. Ventromedial hypothalamic nucleus (VMH) lesion

3.19.1.1. Monosodium Glutamate (MSG)

The administration of monosodium glutamate to newborn rats causes the destruction of the ventromedial hypothalamic and arcuate nuclei, leading the rats to develop obesity due to the lack of control between absorption and energy expenditure.

MSG can be administered subcutaneously or intraperitoneally at doses that vary by 2-4 mg/g of body weight of the rat during the neonatal period and for periods ranging by 4-10 doses causing obesity.

3.19.1.2. Electrical VMH Lesion

The VMH lesion was described by Saito et al (1985) and now, with a few changes, it can be used to induce obesity. A 1.2 mA current lasting 4 seconds, repeated 3 times at 30-second intervals after positioning the electrodes, can cause bilateral destruction of the hypothalamic nuclei, leading to obesity.

As described by Dube et al the injury can also be caused with a single electrical current of 2.5 mA for 15 seconds using stereotactic instruments placing the tip of the rat nose 3.3 mm below the interaural line and positioning the tip of a stainless steel electrode 2.6 mm behind the bregma, 0.5-0.6 mm lateral to the midline and below the base of the brain and raised 0.5 mm.
3.19.2. Oophorectomy

In this model obesity is induced in rats by performing oophorectomy, this is analogous to the observation that women develop number of metabolic changes including weight gain after menopause.

3.19.3. Hypercaloric diets

This is the simplest obesity-induction model, and possibly the one that most closely resembles the reality of obesity in humans. There are several types of diets to induce obesity that have proved effective. A few diets attain hypercaloric values by adding carbohydrates and others by fats, and most of them vary between 3.7 Kcal/g and 5.4 Kcal/g. All of them are highly palatable and induce obesity.

3.19.4. Genetic models

The genetic models to study obesity began to be used increasingly in the 1990s, because of cloning and identification of the product of five different genes causing obesity. Furthermore, in the last few years, genetically modified or knockout animals have been produced to study new genes that are candidates to influence the rate of obesity. There are over 50 different types of genetic models of obesity in rodents.

3.20. GUIDELINES FOR SURVIVAL BLEEDING OF RATS

These guidelines have been developed to assist investigators and NIH Animal Care and Use Committees (ACUC) in their choice and application of survival rodent bleeding techniques. The guidelines are based on peer-reviewed publications\(^{(139-143)}\) as well as on data and experience accumulated at NIH. The Investigator and veterinary staff should decide which method of blood withdrawal to use. As with any procedure, training is critically important. The comfort and level of skill of an investigator with a procedure as well as the sample volume and frequency of sampling should be considered when choosing a method. For example, some institutions recommend the use of retro-orbital bleeding only for specific applications and encourage investigators to use other techniques, whereas other institutions place no restrictions on retro-orbital bleeding performed by trained investigators. It is the responsibility of both the investigator and
ACUC to ensure use of techniques and procedures which result in the least pain and
distress to the animal, while adequately addressing the needs of the experimental design.
Any exceptions to these guidelines, e.g., increase in blood volume to be collected or
retro-orbital bleeding without use of anesthesia as outlined below, must be described in
IC ACUC guidelines or must be scientifically justified in the Animal Science Products
(ASP) and approved by the IC ACUC.

Factors to consider in choosing the blood withdrawal technique appropriate for the
purpose at hand include, but are not limited to:

• The species to be bled.
• The size of the animal to be bled.
• The type of the sample required (e.g. serum, whole cells, etc.).
• The quality of the sample required (sterility, tissue fluid contamination, etc.)
• The quantity of blood required.
• The frequency of sampling.
• Health status of the animal being bled.
• The training and experience of the phlebotomist.
• The effect of restraint or anesthesia on the blood parameter measured.

The acceptable quantity and frequency of blood sampling is dependent on the circulating
blood volume of the animal and the red blood cell (RBC) turnover rate.

The approximate circulating blood volume of rodents is 55 to 70 ml/kg of body weight.
Of the circulating blood volume, approximately 10% of the total volume can be safely
removed every 2 to 4 weeks, 7.5% every 7 days, and 1% every 24 hours\(^{(144,145)}\). Volumes
greater than recommended should be justified in the ASP and appropriate fluid and/or
cellular replacement provided. Blood sample ranges, based on body weight, are provided
in (Table 3.9).
Table 3.9: Approximate blood sample volumes for a range of body weights

<table>
<thead>
<tr>
<th>Body weight (g)</th>
<th>*CBV(ml)</th>
<th>1% CBV (ml) every 24 hrs†</th>
<th>7.5% CBV (ml) every 7 days†</th>
<th>10% CBV (ml) every 2 - 4 wks†</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1.10 - 1.40</td>
<td>.011 - .014</td>
<td>.082 - .105</td>
<td>.11 - .14</td>
</tr>
<tr>
<td>25</td>
<td>1.37 - 1.75</td>
<td>.014 - .018</td>
<td>.10 - .13</td>
<td>.14 - .18</td>
</tr>
<tr>
<td>30</td>
<td>1.65 - 2.10</td>
<td>.017 - .021</td>
<td>.12 - .16</td>
<td>.17 - .21</td>
</tr>
<tr>
<td>35</td>
<td>1.93 - 2.45</td>
<td>.019 - .025</td>
<td>.14 - .18</td>
<td>.19 - .25</td>
</tr>
<tr>
<td>40</td>
<td>2.20 - 2.80</td>
<td>.022 - .028</td>
<td>.16 - .21</td>
<td>.22 - .28</td>
</tr>
<tr>
<td>125</td>
<td>6.88 - 8.75</td>
<td>.069 - .088</td>
<td>.52 - .66</td>
<td>.69 - .88</td>
</tr>
<tr>
<td>150</td>
<td>8.25 - 10.50</td>
<td>.082 - .105</td>
<td>.62 - .79</td>
<td>.82 - 1.0</td>
</tr>
<tr>
<td>200</td>
<td>11.00 - 14.00</td>
<td>.11 - .14</td>
<td>.82 - 1.05</td>
<td>1.1 - 1.4</td>
</tr>
<tr>
<td>250</td>
<td>13.75 - 17.50</td>
<td>.14 - .18</td>
<td>1.0 - 1.3</td>
<td>1.4 - 1.8</td>
</tr>
<tr>
<td>300</td>
<td>16.50 - 21.00</td>
<td>.17 - .21</td>
<td>1.2 - 1.6</td>
<td>1.7 - 2.1</td>
</tr>
<tr>
<td>350</td>
<td>19.25 - 24.50</td>
<td>.19 - .25</td>
<td>1.4 - 1.8</td>
<td>1.9 - 2.5</td>
</tr>
</tbody>
</table>

* Circulating blood volume
† Maximum sample volume for that sampling frequency

The most frequently used survival sampling sites: a) retro-orbital; b) mandibular; c) saphenous; d) tail; and e) jugular. Blood withdrawal by cardiac puncture is considered a euthanasia procedure and should be performed only after ensuring that the animal is under deep anesthesia, as evidenced by lack of response to a painful stimulus (e.g., toe or tail pinch).

3.20.1. Guidelines to Retro-orbital Sinus/Plexus Sampling

i. Retro-orbital sampling can be used in both mice and rats (though not a preferred method in the rat) by penetrating the retro-orbital sinus in mice or plexus in rats with a capillary tube or Pasteur pipette.

ii. Rapid – large number of animals can be bled within a short period of time.

iii. Obtainable volume: medium to large.

iv. Good sample quality. Potential contamination with topical anesthetic, if used, should be taken into account.

v. A minimum of 10 days should be allowed for tissue repair before repeat sampling from the same orbit. Otherwise the healing process may interfere with blood flow.

vi. Alternating orbits should not be attempted until the phlebotomist is proficient in obtaining samples from the orbit accessed most readily by the dominant hand.
a right handed individual should gain proficiency withdrawing samples from the right orbit before attempting to obtain samples from the left orbit.

vii. In the hands of an unskilled phlebotomist, retro-orbital sampling has a greater potential than other blood collection routes to result in complications.

viii. In mice, general anesthesia is recommended if compatible with experimental design. If retro-orbital bleeding is conducted without general anesthesia a topical ophthalmic anesthetic e.g. proparacaine or tetracaine drops, must be applied prior to the procedure.

ix. In rats, the presence of a venous plexus rather than a sinus can lead to greater orbital tissue damage than in the mouse. General anesthesia must be used unless scientific justification is provided and approved by the IACUC. In addition, a topical ophthalmic anesthetic, e.g. proparacaine or tetracaine drops, is recommended prior to the procedure. ARAC believes that retro-orbital bleeding performed in rats by a trained practitioner represents more than “minimal or transient pain and distress” and therefore should be considered a USDA Column “D” procedure.

x. In both mice and rats, care must be taken to ensure adequate hemostasis following the procedure.

xi. Use of sterile capillary tubes and pipettes are recommended for use to help avoid periorbital infection and potential long-term damage to the eye. The edges of the tubes should be checked for smoothness to also decrease likeliness of eye damage.