Obesity in perspective

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Summary

Attitudes to obesity are changing. It is currently regarded as a common, multifactorial disorder with serious medical and psychological consequences. It is also resistant to treatment. Recent research with experimental animals has given new insights into the molecular pathology of this condition and gives some hope of novel therapeutic intervention.

Obesity is a symptom frequently described as the presence of more than 20 - 30% of body weight as fat (mainly triglycerides). It should not be confused with overweight (composed of organ, bone, muscle and fat mass), oedema or mild fatness. The prevalence of obesity in Western society is increasing. It is frequently associated with an increased risk for renal disease, cirrhosis of the liver, heart disease (i.e. sudden death, angina pectoris, congestive heart failure but not coronary thrombosis), gallbladder and endocrine disease, osteo-arthritis, hypertension, diabetes mellitus, gout, subobtimal pulmonary function and impaired life expectancy. Mortality is not a linear function of body weight, but increases dramatically above a certain figure.

Obesity is frequently associated with increased blood levels of free fatty acids, triglycerides, uric acid, glucose and insulin, and with decreased levels and response of growth hormone (increased synthesis of cholesterol has also been reported, although blood levels may be normal). (These parameters are of course influenced by diet and whether the person is in a dynamic or static phase of weight gain.) The socio-economic cost to society is considerable, and it must be emphasized that obesity as defined is a public health problem and not one merely cosmetic in nature. To the individual the cosmetic aspect may, however, represent a severe social and psychological handicap which can dramatically alter his quality of life.

The aetiology of this condition is multifactorial and may involve hypothalamic, neural and neurotransmitter mechanisms and/or genetic, hormonal, metabolic and/or nutritional factors. The primary derangement is an increased caloric intake (metabolizable energy) in relation to caloric expenditure. This may not imply hyperphagia, but may be related to increased caloric density due to dietary pattern or diet, reduced caloric expenditure due to physical or mental inertia, increased fat anabolism due to differential tissue utilization of glucose, or to a more efficient catabolism, i.e. reduced thermogenic capacity.

Obesity therefore represents a syndrome rather than a specific disease. It is not a self-inflicted condition any more than is heart disease or depression, but represents a disturbance in whole-body energy metabolism which may have various aetiological factors.

The syndromes of obesity are: (i) genetic (e.g. Prader-Willi syndrome); (ii) nutritional (diet, eating pattern); (iii) hypothalamic (e.g. tumour); (iv) endocrine (e.g. Cushings syndrome, adult-onset diabetes mellitus); (v) metabolic (distribution and activation of enzymes in various tissues); (vi) hormonal (distribution of receptors in various tissues); and (vii) psychological (reactive obesity). (Genetic and endocrine factors are not dealt with in this review. For excellent recent summaries see Bray and Yank and Bray (autonomic and adrenal hypothesis) respectively. Genetically selected animal models have contributed enormously to the study of obesity.)

These syndromes are not mutually exclusive; several of them may interact to produce the resultant obesity.

Nutritional status and physical exercise are the primary contributing factors to obesity which are recognized by the man on the street (i.e. gluttony and sloth) and indeed by many medical practitioners. Although these factors are present in the majority of cases of obesity encountered, they are possibly overlaid on (for example) a hypothalamic-mediated hyperphagia or on a genetic predisposition which results in an altered metabolic profile and in a person more susceptible to obesity. Established obesity may be maintained in the presence of a 'normal' nutritional intake, and in experimental animals obesity can develop in the absence of hyperphagia.

Areas of the hypothalamus are thought to control hunger (ventrolateral area (VLH)) and satiety (ventromedial area (VMH)). The noradrenergic neurons passing through the VMH area (ventromedial bundle) may be involved in these neuro-endocrine control mechanisms (VMH = a-adrenoceptors; VLH = b-adrenoceptors) and they may interact with the nigrostriatal dopaminergic (VLH) and serotonergic (VMH) neurons. Certain anorexiant drugs have been shown to interact with these neurons, e.g. amphetamines (dopamine, noradrenaline) and fenfluramine (dopamine, serotonin). Gastric distension acting through neural pathways (vagus nerve) represents a crude physiological signal of satiety, although there may be feedback from the gut to the hypothalamus through certain gut hormones, e.g. bombesin, cholecystokinin. Other metabolic products have also been proposed to be involved in metabolic feedback on hypothalamic control of appetite, e.g. short-chain fatty acids, tryptophan. It has also been suggested that glucose or insulin may act on the VMH area (satiety) and increase noradrenergic output while free fatty acids may act on the VLH area (hunger). Opioid receptors in the reward areas of the brain may also be involved in appetite control.

Classification

The obesities have been classified morphologically into two types: (i) hypertrophic (± 80%) - increased size of fat cells (also known as alimentary, social, exogenous, mobile, acquired or late-onset); and (ii) hyperplastic (± 20%) - increased number of fat cells (also known as endogenous, essential, metabolic, hypercellular, pathological, refractory or early-onset).
Hypertrophic obesity is generally of maturity-onset (>30 years of age) and mild. It responds to diet and exercise and is frequently found in lower socio-economic groups. It should be noted that the division into the two types is not clear-cut and not universally accepted. An increase in adipose cell size is present in all forms of obesity and the overall incidence of obesity increases with age (up to 50 years).

Hypertrophic obesity has generally an early age of onset and is more refractory to treatment. The increase in adipocyte cell number is generally not reversible (although this can be achieved temporarily by surgical lipectomy and may occur with 'prolonged weight loss') even in the face of weight loss, which represents a reduction in fat cell size but not in number. This adipocyte hyperplasia represents a significant factor in obesity refractory to long-term treatment. Adipocyte proliferation mainly takes place early in life (<2 years of age) and at puberty (months), but when adipocytes reach a certain size, adipocyte proliferation occurs at any age, and thereafter adipocyte number correlates with the extent of obesity. Therefore while fat infants frequently become fat adults, this is not always the case, although neonatal or infant adipocyte hyperplasia appears to be an increased risk factor for adult obesity. Conversely, hyperplastic obesity has on occasions been shown to be adult-onset in nature, i.e. reactive obesity.

It is a matter of common experience that each adult has the capacity to maintain a fairly constant body weight over prolonged periods. This requires physiological and biochemical feedback of dietary metabolites on hypothalamic regulation of appetite and metabolism (possibly all of these mechanisms operate and this makes weight control on the basis of dietary content difficult as each dietary component may have a reduced capacity for NST and are more sensitive to cold exposure or increased noradrenergic output at thermoneutrality. It has also been suggested that insulin is involved in an effect on NST (whole body) and long-term (other brain areas) control of weight homeostasis, and in stimulation of sympathetic noradrenaline release. None of these hypotheses has been validated, but what is apparent is that during the dynamic phase of obesity the body weight homeostatic mechanisms fail to operate or are overridden.

In practical terms it means that established obesity (static phase) is more refractory to treatment, and that prolonged weight loss is difficult to maintain. This may also be attributed, in part, to the difference in insulin response in adipocytes of varying size (cell >large and to a reduction in thermogenesis on hypocaloric intake).

A further complication is the possibility that the nature of adipocytes (omental or subcutaneous) may not be uniform. This may explain the characteristic distribution of fat found in certain endocrine obese subjects.

**Treatment**

Obesity (particularly hyperplastic) represents an extremely demanding therapeutic challenge. Most physicians, while not completely in agreement with many widely publicized diets, recommend caloric restriction on a balanced or supplemented diet, mild aerobic exercise, and behavioural therapy for mild obesity. Specific dietary restriction (i.e. popular diets) can increase individual motivation and give an easy method for individual determination and control of caloric intake, and the reduction in food variety reduces palatability and appetite but can lead to dietary deficiency states. The importance of mild exercise should also be stressed. The increased prevalence of obesity in handicapped groups suggests that lack of exercise may not only be a symptom characteristic of obesity, but also contribute to its development. While exercise as a treatment of obesity may have little impact on overall energy expenditure (basal metabolism, i.e. maintenance of vital cell functions, accounts for the major part (60 - 70%) of energy utilization), it may alter hormonal or metabolic factors and relieve secondary changes of obesity, e.g. insulin resistance, or cause prolongation of 24 hours post-exercise changes in metabolic rate which may contribute to continuing weight loss.

Psychological or environmental factors may also play a role in the development of obesity. While normal people tend to start (hunger signal) and stop (satiety signal) eating in response to internal physiological stimuli, indications are that obese people tend to respond more readily to external appetite stimuli, i.e. smell, taste and presentation of food. Such factors may override internal hunger and satiety signals.

These internal signals may be manipulated with anorexiant drugs, and their use (when recommended) is as a supplement to hypocaloric diets, but behavioural therapy is important in long-term weight loss, particularly as repeated unsuccessful attempts at weight loss can alter metabolic response with the increased likelihood of the development of more severe obesity in the future, i.e. 'rebound effect' or 'adaptive hyperlipogenesis'. Such episodes are also disheartening for the individual. Behavioural therapy aims to reinforce altered activity patterns and lifestyle (it is difficult to contemplate eating only pineapples for the rest of your life!), to change priorities and gratification signals, and to build a better hunger response, self-confidence and a sense of personal responsibility.

Therapy with anorexiant drugs, thyroid hormones or biguanides is controversial and should be carried out under close medical supervision, or after firm diagnosis of (for example) hypothyroidism. Surgical intervention by intestinal bypass, gastric banding or jaw wiring is recommended only for grossly obese patients and these procedures are normally carried out in specialist clinics and preceded by procedures to reduce oedema, improve respiratory function and establish metabolic homeostasis. While intestinal bypass has a good short-term weight loss, it has many serious long-term side-effects. Suction lipectomy should be performed by an experienced plastic surgeon and it is intended more as a cosmetic procedure than as a treatment of obesity.

At the present time it must be stated that the results obtained in the treatment of obesity are disheartening for both therapist and subject. Nevertheless, more recent experiments with animal models have given rise to new insights into the molecular pathology of obesity which may find application in humans, and gives some hope for novel therapeutic intervention in the near future.

While the first half of this presentation dealt mainly with calorlic intake, the second part will deal mainly with caloric expenditure.

**New horizons**

**Thermogenesis**

The role of thermogenesis in body-weight homeostasis was first suggested by Rubner in 1902. Temperature homeostasis in man is controlled by areas of the hypothalamus, and production of thermal energy is linked to oxygen consumption and to the efficiency of generation or utilization of adenosine triphosphate (ATP). After a meal there is an increase in body temperature due to the processes of digestion and absorption. This has been called the specific dynamic action of food. It has often been equated with dietary-induced thermogenesis (DIT), although the latter effect is more prolonged and depends on the nature of the food and the metabolic fate of the absorbed nutrient. The DIT of food will be treated here as heat generation distinct from what is known as adaptive or regulatory thermogenesis (AT) (this has also been suggested to be a component of DIT), although the former is now more commonly referred to as non-shivering thermogenesis (NST). AT is a metabolic response to cold stress which is distinct from shivering thermogenesis (ST), which is a neuromuscular response to sudden cold exposure. NST (SST) has features in common with the action of noradrenaline at thermoneutrality. It has been shown that genetically obese mice have a reduced capacity for NST and are more sensitive to prolonged exposure to reduced temperature. In the presence of cold exposure or increased noradrenergic output at thermo-
Hypothyroid rats have also been shown to have adipose tissue and BAT. Although BAT contains only 2% of body weight in humans, 30% of the increase in total cardiac output is diverted to this tissue in rats under the influence of noradrenaline, and more than 60% of the excess oxygen consumed (increased metabolic rate) is taken up by BAT. Cold acclimatisation has been shown to increase the number of BAT cells in areas of mice normally associated with white adipocytes, and Rothwell and Stock have demonstrated an increased thermogenic response to noradrenaline in cafeteria-fed obese rats during the period of subsequent weight loss (22 days). BAT is highly vascularized and innervated, and stimulation by noradrenaline is via sympathetic nerves and BAT beta-receptors. It may also be regulated by the VMH area of the brain.

It has been proposed that altered blood flow gives rise to tissue-specific (BAT) metabolism and oxygen consumption. Blood flow to the heart, diaphragm (respiratory muscles), skin and white adipose tissue of mice is increased after administration of noradrenaline.

BAT thermoregulation is derived from beta-oxidation of fatty acids by BAT mitochondria and the uncoupling of subsequent oxidative metabolism may contribute to the development of brown adipose tissue (BAT) thermoregulation which they suggest will give increased sensitivity in metabolic regulation, and may produce heat as a side-effect of ATP consumption. The term "futile cycles" has been used to describe these metabolic pathways. The concept applies to independent (non-equilibrium) forward and reverse reactions where ATP is consumed and heat is generated in an exothermic (reverse) reaction. (It is through such reactions that heat is generated for the flight of the bee.) These cycles have two components necessary for cycling activity and the relative rate of each reaction (i.e. forward and reverse) controls the flux through or across the cycle, and the rate of cycling. The rate of cycling controls the heat generated, e.g. simultaneous high levels of insulin (forward reaction) and noradrenaline (reverse reaction) could give a low cycle flux, a high cycling rate and substantial heat production (Fig. 1).

Newsholme and Newsholme have proposed a further component of thermoregulation which they suggest will give increased sensitivity in metabolic regulation, and may produce heat as a side-effect of ATP consumption. The term "futile cycles" has been used to describe these metabolic pathways. The concept applies to independent (non-equilibrium) forward and reverse reactions where ATP is consumed and heat is generated in an exothermic (reverse) reaction. (It is through such reactions that heat is generated for the flight of the bee.) These cycles have two components necessary for cycling activity and the relative rate of each reaction (i.e. forward and reverse) controls the flux through or across the cycle, and the rate of cycling. The rate of cycling controls the heat generated, e.g. simultaneous high levels of insulin (forward reaction) and noradrenaline (reverse reaction) could give a low cycle flux, a high cycling rate and substantial heat production (Fig. 1).

Adipocyte homeostasis has often been discussed in terms of the lipogenic effect of insulin and the lipolytic effect of noradrenaline/adrenaline (adrenocorticotropic hormone, thyrotrophin and glucagon are also lipolytic). It is now known that there are four different types of adipocytes in human white adipose tissue -- beta, beta alpha, omega and delta. (This topic has recently been reviewed in depth by Kather and Fain and Garcia-Sainz and will be discussed only briefly.) Adrenaline originates mainly in the adrenal medulla, and noradrenaline is released from sympathetic nerve endings. The role of this "sympatho-adrenal system" in obesity has recently been reviewed by Landsberg and Young.

The beta-receptors (adrenaline noradrenaline) are linked to the adenylate cyclase system and to the stimulation of lipolysis, and this effect is inhibited by insulin. The beta-receptors (adrenaline noradrenaline) may be linked to the methylation of certain phospholipids, and possibly to eicosanoid biosynthesis, although this is not conclusive. The ratio of beta to beta receptors may vary with adipocyte cell maturity, but both types are present in mature adipocytes. The alpha-receptors (noradrenaline) are coupled to the phosphatidylinositol cycle and to alterations in intracellular levels of eicosanoids and calcium. They are the predominant catecholamine receptors found on hepatocytes and they regulate glycogen metabolism, i.e. inhibit glycogen synthetase, but they have no established role in adipocyte lipolysis. They are absent in subcutaneous adipose tissue but are present in omental adipocytes.

The alpha-receptors (adrenaline) are also coupled to the adenylate cyclase system. While beta-stimulation increases cyclic adenosine monophosphate (cAMP) levels and lipolysis, alpha-stimulation lowers intracellular cAMP and inhibits lipolysis. In man, alpha-adipocyte responsiveness has been shown to be increased in areas of preferred fat deposition, e.g. hip and gluteal regions. The ratio of beta to alpha receptors and their individual responsiveness may be influenced by thyroid hormones, i.e. hypothyroidism decreases beta-receptor response, hyperthyroidism decreases alpha-receptor response. Hypothyroid rats have also been shown to have increased levels of CAMP phosphodiesterase, increased transport of hexoses into adipocytes and decreased levels of serum growth hormone. The alpha-receptor responsiveness is (paradoxically) increased in fasting subjects.

While beta and alpha-receptor stimulation may influence intracellular eicosanoid levels, the eicosanoids also have their own adipocyte cell surface receptors. At nanomolar concentrations (in the presence of guanosine triphosphate) prostaglandin (PG) E, is a potent inhibitor of catecholamine-induced lipolysis, while PGE, and micromolar concentrations of PGE, stimulate lipolysis.

Scharmann et al. and Curtis-Prior have proposed that PG metabolism may play a role in obesity, and may offer an area for therapeutic intervention.

Adipose tissue metabolism is obviously complex, and despite apparent morphological homogeneity, at the molecular level white
adipocytes are heterogeneous. To complicate the picture further, insulin (in the absence of calcium) has been shown to increase intracellular levels of the breakdown products of the phosphati-
dylinositol cycle, and non-hormonal factors can affect catechola-
mine actions on lipolysis, e.g. cholela and pertussis toxin, forskolin.

The four types of adrenoreceptors are probably present in BAT, although the presence of \( \beta \)-receptors is not conclusive. Stimulation of hamster BAT \( \alpha \)-receptors stimulates respiration, and the \( \beta \)-
receptors on BAT of rats stimulate lipolysis, respiration, cAMP formation, and thermogenesis and may be influenced by thyroid hormones.\(^{58,59}\)

Insulin and the respiratory control of metabolic fate

The preceding sections suggested that a more efficient catabolism (i.e. defect in thermogenesis) or change in the catecholamine/eicosanoid control of lipolysis may be present in obesity. A further possibility is that there is a more efficient or increased fat anabolism (i.e. lipogenesis). That is a shift in tissue (muscle \( \rightarrow \) adipocyte)\(^{1,45,66}\) and metabolic priorities. Hyperinsulinemia and peripheral insulin resistance are often found in obesity. This resistance is not easy to define (generally as decreased clearance of glucose from the circulation), and it may apply to specific tissues. Whole-body measurements of metabolic rate or reduced clearance of glucose from plasma are difficult to interpret in this respect, and the ultimate metabolic fate of glucose used as a measure of post-insulin-receptor metabolism will influence conclusions drawn. Insulin has been shown to increase glucose utilization for esterification of fatty acids in large adipocytes.\(^{66}\)

It has been demonstrated in the fetus that hyperinsulinism gives rise to hypoxia,\(^{5,6,70}\) and it has been suggested that this hypoxia may modify glucose metabolism and increase glyceral-3-phosphate synthesis in white adipose tissue by shunting glucose through the hexose monophosphate shunt pathway.\(^{6,12}\) This may be an attempt to clear circulating glucose in a manner conservative with respect to oxygen consumption. The contribution of the hexose monophosphate shunt pathway to glucose metabolism in isolated rat adipocytes has been shown to be increased by insulin and decreased by noradrenaline\(^{64}\) and growth hormone.\(^{53}\) Increased export of very-low-density lipoprotein (VLDL) from the liver has been observed in obese rats\(^{16}\) and increased transport of this VLDL to adipocytes would result in increased levels of adipocyte fatty acids, and in the presence of increased glyceral-3-phosphate, increased triglycerides, i.e. adipocyte hypertrophy. Insulin has been shown to increase adipocyte lipoprotein lipase activity,\(^{67}\) and lipoprotein lipase activity\(^{57}\) and fasting insulin levels\(^{59}\) have been correlated with fat cell size. Respiratory embarrassment is also present in gross obesity, and it has been suggested that this may be related (exponentially) to the degree of obesity.\(^{64}\)

Thermogenesis (BAT, NA-K-ATPase and futile cycles) also requires oxygen. Therefore oxygen utilization and the ultimate tissue and metabolic fate of glucose may depend upon the availability of oxygen and on the ratio of insulin: catecholamines, although many other factors may act as fine controls, e.g. thyroid hormones. Oxygen itself may exert a respiratory control on the action of hormones,\(^{40}\) and it is interesting to speculate on the effect of oxygenation on eicosanoid metabolism in the microcirculation,\(^{51}\) as these compounds have potent vasoactive properties and are an important part of the cell second messenger system.\(^{68}\) Hypoxia is frequently found in grossly obese patients (e.g. pickwickian syndrome), and a mechanism along the lines suggested may contribute to a vicious cycle of hyperinsulinism, respiratory compromise, reduced thermogenesis, increased triglyceride synthesis, continuing weight increase and obesity refractory to treatment.

Treatment

Experiments are continuing with centrally acting (noradrenergic neurons), non-amphetamine appetite suppressants, e.g. mazindol (Toremuc; Wander), and sustained weight loss (± 12 months) on a hypocaloric diet has been demonstrated.\(^{6,2}\) In man fenfluramine, besides its effects on the central nervous system, has been shown to increase uptake of glycine into muscle in preference to adipose tissue (an action which mimics the effect of mild exercise).\(^{63}\)

Attempts have been made at dietary manipulation of thermo-
genesis (high-carbohydrate/low-protein diet),\(^{6,4}\) or eicosanoid levels (evening primrose oil),\(^{6,5}\) but without obvious therapeutic potential at this stage.

The complexity of adrenoreceptors in adipose tissue and the fact that they are not exactly similar to those in other tissues\(^{7,18}\) has led to the development of specific adrenergic agonists. Yen et al.\(^{6,6}\) have recently used a \( \beta \)-receptor agonist (LY 79771) to reduce body weight and increase metabolic rate, thermogenesis and lipolysis in obese mice. The drug did not inhibit appetite. Arch et al.\(^{6,7}\) and Arch and Ainsworth\(^{8,8}\) have used a \( \beta \)-adrenergic agonist (BRL 26830A) which is specific for BAT of rats. It has been shown to stimulate thermogenesis and reduce body weight in genetic, gold thioglucose- and cafeteria-fed obese rats. The drug had no effect on their lean counterparts.

Recent studies by Triscari and Sullivan\(^{9,9}\) in rats have focused on a novel inhibitor of hepatic fatty acid synthesis (R022-0654). Weight gain was decreased in lean and obese rats and could be accounted for by a decrease in total body lipid. Appetite was only transiently affected.

Knoll\(^{10,10}\) of Budapest has described a naturally occurring glyco-
protein (satietin) which is non-addictive, does not affect body temperature and has anorexic properties.

A further mode of approach is through the in vitro culture work with pre-adipocytes which is being done in many laboratories.\(^{11,12}\) The results may shed some light on the process of adipocyte proliferation. Some preliminary work suggests that a serum-derived factor may initiate the process.\(^{51}\) This has obvious therapeutic potential.

Hyperinsulinemia is frequently present in obesity, and in some cases may contribute to the condition. Attempts are being made\(^{13,14}\) to synthesize somatostatin analogues (e.g. WY-18166, Wyeth Laboratories) which specifically inhibit insulin release and do not affect release of growth hormone or glucagon. Some preliminary work has also been done by Yen et al.\(^{9,9}\) (Eli Lilly Research Laboratories) using dehydroepiandrosterone, which inhibits glucose-6-phosphate dehydrogenase activity (rate-limiting enzyme in hexose monophosphate shunt pathway), and it has been shown to reduce body fat in growing obese mice.

Conclusion

It is now realized that obesity is enormously more complex than was previously thought. Homeostatic body weight mechanisms make it difficult to treat, although recent research gives some hope for therapeutic intervention in the near future. The study of obesity and adipocytes is continuing to shed light on physiological, hormonal and metabolic mechanisms which may have application not only to adipocytes and obesity, but to many other cell types and to many diseases. These studies are concerned with such basic problems as the control of cellular proliferation, the tissue-specific utiliz-
ation of substrates, alterations in blood flow to and oxygen status of specific tissues in vivo, and alterations at the second messenger level which will ultimately control cellular behaviour and intracellular metabolic fate. The unravelling of the molecular pathology of obesity will undoubtedly give answers with far-reaching consequences.

REFERENCES

Neurobehavioural effects in rats fed low doses of cadmium and lead to induce hypertension

C. J. LOCKETT, W. P. LEARY

Summary

Rats given diets supplemented with low doses of cadmium or lead or both elements together showed an increase in cadmium levels within the brain in all supplemented groups. Hypo-activity was noted after 16 months of dietary supplementation with lead or with cadmium and lead. Activity was unaffected by feeding with cadmium alone.

Effects of cadmium on the central nervous system

The administration of cadmium results in decreased activity of the Na,K,Mg-dependent ATPase of brain, both in vitro and in vivo. In increasing doses cadmium abolishes reflexes, then the sensation of pain, and finally causes death by asphyxia due to pulmonary oedema. It has been suggested that the marked prostration, flaccidity of muscles and respiratory paralysis observed in rats after intravenous injections of toxic doses of cadmium may be due to displacement of calcium ions from their action sites.

Aims

The objective of the present experiment was to examine the relationship between brain trace element levels and neurobehavioural activity, using an animal activity monitor, in...