Cell

How to Stop the Obesity Epidemic?

Ice Breaking

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China has entered the era of obesity. Data from China Noncommunicable Disease (NCD) Surveillance 2010 have shown that one in three Chinese adults had either central or general obesity. Meanwhile, the epidemic of childhood obesity may weigh on China's future. Obesity affects virtually all ages and socioeconomic groups and significantly contributes to the rocket-rising incidence of NCDs, including type 2 diabetes, cardiovascular diseases, and certain forms of cancer, which is worrisome for a country with a population of 1.37 billion.

The huge demographic pressure, unbalanced economic development, unmet social diversity, and childhood obesity epidemic have all created tough challenges for the Chinese government to fight against obesity. Prevention and control strategies must be comprehensive and should include proactive approaches: reducing health disparity through healthcare reform and development, protecting parental and childhood health, enhancing education on a healthy lifestyle, implementing awareness and detection programs for genetically susceptible individuals, and early interventions targeting high-risk population. To efficiently halt the obesity epidemic, the main focus should be placed on children and adolescents. The national research supporting systems should encourage biomedical scientists to explore the pathogenesis of obesity and develop safe and effective novel anti-obesity drugs/procedures toward gut microbes, brown fat, and genetic targets in regulatory network of metabolism. International cooperation is of key importance in basic research and translational studies. It is tough, but with hope.

Move It and Lose It

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There is a growing health burden arising from the interrelated sequelae of metabolic disorders comprising impaired glucose tolerance, type 2 diabetes, and sarcopenia. Obesity and physical inactivity are the main drivers of these metabolic disorders, with the risk of co-morbidities including hypertension, dyslipidemia, cardiovascular disease, stroke, cancer, sleep apnea, gallbladder disease, hyperuricemia and gout, and osteoarthritis. A critical health issue facing overweight adults is how to lose fat mass and improve whole-body glucose tolerance, while simultaneously preserving skeletal muscle mass. This goal is made especially difficult in the face of reduced levels of physical activity and increased longevity.

Modifiable lifestyle factors such as exercise training and diet are clinically proven, cost-effective, primary interventions that delay and, in many cases, prevent the health burdens associated with obesity. Yet, achieving this is easier said than done, and inertia is difficult to overcome. The principal challenge is to find "practical, ready-to-use" solutions to combat the growing epidemic-like increase in metabolic disease. This could be through the development of time-efficient, lifelong exercise intervention strategies that include dietary modifications. Importantly, these modifications must be readily incorporated into an individual's "everyday routine." A second goal is to provide clinical insight into the heterogeneity underlying not only the development of metabolic disease, but also individual differences in the response to treatment regimes. Given the widespread benefits of regular physical activity, it may be better to be fit and fat than lean and lethargic.

Research, Not Surgery

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As a physician-researcher in the field of diabetes and obesity, I am struck each year by the statistics showing the increasing prevalence of overweight and obesity and one of its major results, type 2 diabetes, with almost a million more cases each year in the U.S. alone. At the same time, I am struck by the great advances in research on cellular/molecular mechanisms underlying the control of energy balance through regulation of appetite and energy expenditure. The data are clear that the driving force in this epidemic is increasing levels of energy intake (168–335 kcal/day between 1970 and 2000), coupled with decreasing energy expenditure due to sedentary lifestyle. As one of my obese patients said, "Doc, I am digging my grave with my mouth." How are we going to change this trajectory? History has shown that changing behavior is difficult. Bariatric surgery works, but even in the best centers, surgical mortality rates are about 1 per 1,000—a level higher than we would ever accept for a medical therapy. So we have to find ways to convert our research into practical solutions. There are at least three areas of real hope: (1) unleashing the power of anorexigenic hormones, including hypothalamic, adipose-derived, and gut hormones; (2) stoking the fire of energy expenditure through agents that activate or increase the mass of brown/beige fat; and (3) finding the composition of gut microbiota that minimizes the impact of caloric excess on weight gain, insulin resistance, and metabolic dysfunction. With these, we can begin to stem the rising tide of obesity and its associated metabolic complications.

Fat Is Not Your Enemy!

Bruce Spiegelman
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Obesity is defined as a condition of excessive fat mass, but what do the fat cells do in normal physiology and in pathological states like obesity? White adipose tissue (ordinary fat) represents the major site for storage of chemical energy in mammals. When there is an imbalance between energy intake (eating) and energy expenditure (exercise, normal cellular processes, and thermogenesis), most of that excess energy is stored as triglycerides in fat. This is the proper and healthy place for energy storage, as lipid deposition in non-adipose tissues such as liver or muscle can impair their function. This occurs with adipose cell dysfunction (lipodystrophy) or when the excess energy simply overtakes the capacity of the fat to store those calories, as in many obese humans. A critical idea that emerged in the 1980s–90s was that adipose tissues are a critical "information hub" and signal metabolic status to the rest of the body through secretion of "adipokines," such as TNF-α, leptin, adipsin, and adiponectin. These affect insulin sensitivity, feeding behavior, and β cell function.

Recently, much attention has been focused on brown and beige adipocytes, thermogenic cells that exist in both rodents and humans. These cells dissipate chemical energy in the form of heat via uncoupled respiration. Increases in amounts of brown and beige fat have been shown to protect against obesity and diabetes in rodent models; strenuous efforts are now being undertaken to learn how to expand or activate these depots in ways that might be therapeutic in humans.

The Secrets of Outliers

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Successful efforts in obesity prevention will require major changes to the obesogenic environment that will be easier to enact in some societies than others for cultural and political reasons. Even with such changes, however, there will still be some individuals who are susceptible to morbid obesity and others who develop catastrophic metabolic decompensation. To treat these people, we will need improved medicines. A foothold toward improved therapeutics has come from studies of human outliers who carry highly penetrant mutations. These studies have been enormously helpful in providing a "wiring diagram" for how processes such as energy balance or the maintenance of insulin sensitivity are regulated in humans. In metabolic disease, there are powerful recent examples of how the discovery of the causative genetic defect in very rare outliers for phenotypes such as bone density or serum cholesterol has directly led to the development of exciting therapeutics. In the area of obesity, leptin is a life-saving therapy for the rare children congenitally lacking the hormone and of great benefit to many more patients with lipodystrophy. We still lack comparable transformative therapies for commoner forms of obesity, however, which may in part be because many of the drug targets revealed by human genetics are in the brain, making them difficult to target. Nevertheless, I predict that human genetic studies of outliers for phenotypes such as extreme leanness and retention of normal insulin sensitivity despite massive obesity will be a fertile ground for the discovery of new targets of great therapeutic promise.

Brain behind Feeding

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Over the last 20 years, the field of obesity research has been revolutionized through the identification of important molecular pathways controlling energy homeostasis. This was pioneered by the identification of leptin as a fuel sensor providing feedback information to the CNS about energy availability in the periphery of the organism to adapt food intake and energy expenditure. This led to the identification of critical neurons that mediate the anorexigenic effects of leptin and that at the same time orchestrate multiple pathways in fuel homeostasis, including glucose metabolism. The recent developments in neurocircuitry mapping, including optogenetics, pharmacogenetics, and translational profiling of defined neurons, provide the basis for a complete understanding of the complex neurocircuitry controlling feeding, energy expenditure, and peripheral glucose metabolism, as well as the integration of these processes with higher cognitive functions. Defining the neuronal convergence points of these regulatory pathways and new modulators of this activity in my view holds the potential to develop a whole range of novel therapeutic targets for metabolic disorders. Moreover, having identified novel pathways involved in obesity through genome-wide association studies has revealed additional regulators of energy homeostasis. Defining their cellular and molecular actions will potentially open novel therapeutic routes as well. Collectively, we are facing an exciting era in obesity research with unprecedented promise for a deeper understanding of its pathophysiology and a plethora of unexpected therapeutic options.