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Are We Fighting a Losing Battle Against Obesity?

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Obesity is defined as a body mass index (BMI) of 30 or greater. The worldwide prevalence of obesity is rising at an alarming rate. In the USA, 17.1% of children and adolescents are overweight and 32.2% of adults are obese; obesity and its co-morbidity lead to over 400,000 deaths and cost more than $150 billion per year [1-3]. The prevalence and trends in obesity in other developed countries are similar to those in the USA. Globally, there are at least 300 million obese adults. Effective treatment options are limited. With diet, about 50% of patients regain weight within one year and almost all patients regain weight within 5 years [4]. The outcome of the medical treatment is not promising due to either adverse effects or lack of long-term efficacy [5-9]. Surgical treatment is the only long-lasting effective therapy; however, it is typically reserved for patients with morbid obesity due to involved surgical risks and complications [10]. Since it is irreversible, surgical treatment causes a big problem to non-responders.

Pharmacologically, are we fighting a losing battle against obesity? Pharmacotherapy is usually effective and typically the first line of choice in treating most other chronic diseases, why does it fail to produce satisfactory results in treating obesity? Since 1930s, more than one dozen of medications have been developed for obesity; however, currently, Orlistat is the only drug that is still available in the market [9]. All other drugs have been withdrawn due to their inefficacy or side-effects. In many cases, the withdrawals of the medications were attributed to a low benefit/risk ratio, mainly due to low efficacy in reducing body weight. The majority of anti-obesity drugs were developed to suppress appetite, while some were targeting metabolic rate or fat absorption [9] by tackling one specific hormone or neurotransmitter or pathway associated with satiety, appetite or energy expenditure. Why did these well-designed compounds fail to produce expected weight loss?

Although evidence is lacking we speculate that the failure of medical therapy is related to human evolution. While the human body system has been evolved to be more and more adapted to environment, in most cases, towards perfection, the evolution of mankind is believed to protect us from starvation or losing weight. Intuitively, we believe that there exist numerous known and unknown mechanisms or pathways that would be activated to compensate for weight loss.

The mankind has evolved to have an accurate and delicate system to remain weight via complicated and multiple mechanisms. The mankind has a known history of at least 50 thousand years and this is a history of continuous fighting against starvation. In contrast, obesity has only been a problem of 30 years or less for developed or some developing countries. Even in this modern world, there are still many places where man is suffering starvation and there is a shortage of sufficient food. Consequently, the human body is believed to have been evolved to prevent from weight loss instead of weight gain. While exact mechanisms for the prevention of weight loss are not clear or unknown, ample evidence has indicated that the physiological system of the human body for the control of energy balance has been evolved to be extremely complicated and accurate. For a healthy adult, the body weight can be maintained at a certain level for many years with little fluctuations. It is known that the amount of annual calories one consumes is about 912,500 kcal (assuming a daily intake of 2,500), whereas, a positive balance of 3,500 kcal can lead to a gain of 1 pound in body weight. One can easily figure out the accuracy of the control system in maintaining a steady weight. This precise control of energy balance is known to involve multiple mechanisms and pathways [11].

The failure in developing effective long term medical therapy as well as the failure of behavioral modification is believed to be attributed to multiple compensatory mechanisms/pathways evolved to protected weight loss. Typically, diet and exercise are the first-line interventions for treating obesity. While short-term results are commonly good, long-term outcomes are poor: 95% or more of patients regain weight within 2 to 5 years [11]. Recently, it was reported that ghrelin, an orexigenic hormone, was increased after short-term weight loss and declined soon after weight gain, demonstrating a compensatory mechanism of the human body to protect weight loss as ghrelin is also known as a hunger hormone which peaks right before a meal and declines after the meal [12]. The elevation of ghrelin after weight loss makes the patient hungry and search for food. In addition to the behavior modification, a number of medications have also been developed for treating obesity [13]. Typically, a medication targets one specific pathway or one specific receptor involved in the regulation of food intake or absorption. Unfortunately, drugs with one specific target are easy for the human body system to compensate for weight loss and consequently, all of these drugs are minimally effective and the effect is typically short term [9]. For example, Orlistat blocks absorption of dietary fat and results in a weight loss of 10% within first 6 months but less than 5% in two years [14]. Sibutramine acts on the central nervous system to reduce energy intake and increase energy expenditure, but its efficacy has also been limited to short term [15]. The unsatisfactory outcomes of these therapies suggest that the human body has a protective mechanism against long-term weight loss and there are compensatory mechanisms and/or redundant pathways to prevent weight loss. The list showing the ineffectiveness of compounds that target one particular hormones or neuropeptides is lengthy. For example, acute administration of peptide YY_{3-36} was reported to reduce food intake by 30% but no effective medications have been developed involving YY_{3-36} [16]. Cholecystokinin (CCK) was discovered to be a satiety signal and found effective in reducing food intake in various animal models; however, this inhibitory effect was reported to disappear rapidly (within 2 weeks) in humans [17].

Are we fighting a losing battle against obesity? Bariatric surgery has given us some insights. Based on major actions/mechanisms, bariatric surgical procedures may be classified into two categories: restrictive and metabolic. The restrictive bariatric surgical procedures, such as lap-band, force the patient to change his/her eating behaviors, resulting in lasting weight loss, whereas, the metabolic surgical procedures, such

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as gastric bypass, involve multiple mechanisms. The most efficacious and long-lasting approach among the bariatric procedures is roux-en-Y gastric bypass (RYGB). In one series, the mean weight loss at 15 years post the RYGB was 29.5 kg [10]. Why this particular approach is superior to other methods of treatment? One interesting thing to note is its mechanisms. Unlike the medication therapy, multiple mechanisms have been identified with the procedure of the RYGB. Firstly, the RYGB restructures the anatomy of the stomach by the creation of a small gastric pouch, which limits food intake; Secondly, 90% of the stomach, the entire duodenum and the proximal jejunum are bypassed, thereby reducing absorption; Thirdly, the bypass of the duodenal and the proximal jejunum accelerates the transit of nutrients to the ileum and thus enhances the inhibitory effect of ileal brake which is known to slow the digestive process [9]; Last but not the least, an increase in peptide YY and glucagon-like peptide-1, anorexigenic hormones, and a decrease in ghrelin have been reported after the procure of RYGB [18]. The encouraging results on long-term weight loss and the multiple mechanisms reported in the literature with the RYGB seem to suggest the importance of multiple mechanisms.

To win the battle against obesity, we may have to develop therapies that involve multiple mechanisms/pathways. A therapy involving multiple mechanisms or pathways may become difficult for the human body system to compensate and/or to react accurately or quickly. In other words, therapies with multiple mechanisms/pathways may dodge the protective mechanisms of the human body and therefore yield long-term weight loss. Similarly, therapies combining different approaches may be more effective in treating obesity than mono-therapies. The advantage of combined medical therapy has been reported in the literature. In an early study, the combination therapy with phentermine and fenfluramine was reported to result in significantly more weight loss than placebo [19]. As another example, fluoxetine was reported to be ineffective in reducing body weight in most random clinical trials but found effective when it was used in combination with dexfenfluramine [20]. Similarly orlistat in combination with amylin analogue pramlintides has been reported to produce promising results on weight loss [21]. Recently, a number of clinical trials have been performed using combinational medical therapies with significant weight loss, such as Bupropion Plus Naltrexone [22], Bupropion Plus Zonisamide [22,23], Topiramate Plus Phentermine [24,25] and Pramlintide Combination Therapies [21,26,27].

In conclusion, obesity is one of the major epidemic diseases affecting millions of people around the world with a lack of effective and safe treatment methods. Since the human body has been evolved to protect us from starvation, the treatment of obesity is difficult and challenging. In our opinion, an effective therapy for obesity, whether medical, surgical or instrumental, should be designed and developed to involve multiple mechanisms/pathways.

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