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Analyzing the past to understand the future of anti-obesity therapeutics

Causes for obesity are not only related to the amount of food we intake and how much exercise we make. There are some people that have faster metabolisms, therefore are less likely to suffer from obesity and people with genetic predisposition for accumulating weight.

Obesity is an epidemic condition that leads to other severe health problems, such as heart diseases, diabetes, cancer, osteoarthritis, high blood pressure, among others. This highly impacts the quality of life of the patient and their families, but it also requires medical treatment that comes at heavy costs for the government.

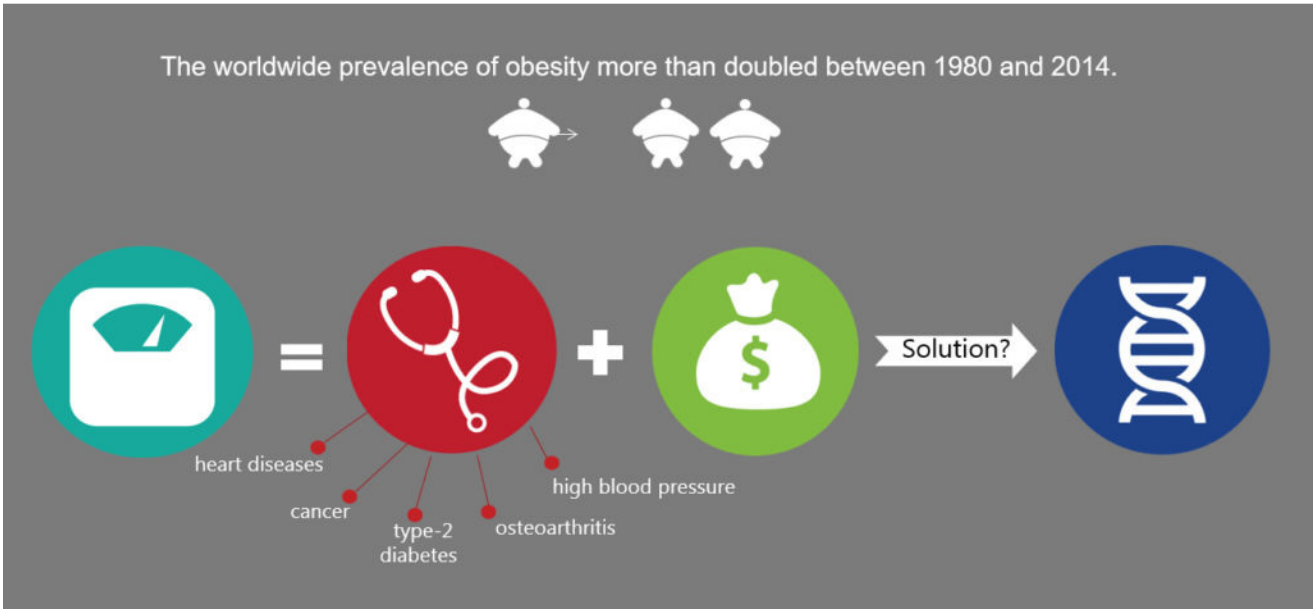

Fig. 1. The worldwide prevalence of obesity more than doubled between 1980 and 2014.

With an increasing number of obesity cases over the last decades, it is urgent to understand the condition, in order to find a treatment. Thus, researchers have been committed to explaining the genetics of obesity. This lead to the study of proteins in the cell membrane and more particularly a subset of those proteins called melanocortin receptors (MCRs). That family of five receptors has been subject to understand their physiological roles. Interestingly when silencing the melanocortin receptor 4 (MC4R) in mice, an increase in body fat tissue, insatiable appetite, and type-II diabetes was observed.

This receptor is naturally regulated by hormones, such as the melanocyte stimulating hormones (MSH). Naturally, these were the first to be investigated as potential anti-obesity therapeutics. However, undesired side effects were registered. In order to selectively activate MC4R, researchers have been looking for a molecule that can bind to the receptor pocket, which will start the signaling cascade until the cell nucleus and, subsequently adjusting the body responses.

We have compiled all molecules that registered more activity at lower concentrations and that were specific for the MC4R when compared to other MCRs. Those molecules, called MC4R agonists, can be divided into two large groups: the peptides and the non-peptide agonists. By comparing all structures, perhaps not surprisingly, we realized how heavily they related to the natural hormones. MSH has a core repeating unit of four amino acids, that has been the source of inspiration for several of this agonists. By itself, this core unit does not show much specificity, but when modified it can become more potent and more specific. Peptide sequences have in average seven amino acids and, when compared to the α-MSH (product of MSH), histidine is the residue that tolerates more modifications, while the conformation changes of phenylalanine (to D-phenylalanine) has been proven to give better interaction with the receptor. Changes in the other two residues of this four-unit core (arginine and tryptophan) have generally resulted in weaker structures. Furthermore, cyclization of the peptide agonists, aside from higher stability, is also beneficial for the receptor-agonist interaction. When it comes to non-peptide structures, there is still heavy use of the amino acids present in the core structure of α-MSH and structures that closely resemble the side chain of such amino acids.

Melanotan-II and Bremelanotide, are structures that showed very promising initials results but failed during clinical trials. Other drugs, namely Setmelanotide and PL-8905 are currently under clinical trials.

Since the discovery of the receptor, several milestones have been achieved, however, there are still some unknown factors. Majority of the studies have considered monomeric structures as the target, but higher ordered multimers, mainly dimers, must be considered. Also, some evidence for a secondary activation pathway has been registered.

While clinical evaluation of novel molecules and a more concrete elucidation of the receptor structure are both warranted and necessary, there appears to be cause for optimism for the promise of α-MSH analogs as therapeutics for obesity management.

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