Pharmacological treatment of obesity: the past, the present and the future

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Introduction

The epidemic of obesity is now recognized as one of the most important public health problems facing the world today.

Overweight	• BMI index ≥ 25 kg/m^2
Obese	• BMI index ≥ 30 kg/m^2

Overweight and obesity, are the fifth most common risk factors for death. Moreover they are predisposing factor to develop other disorders such as dyslipidaemia, hypertension or diabetes type 2 and cardiovascular disease among other. It has also been related to some cancer and with physiological problems including depression and low self-stem.

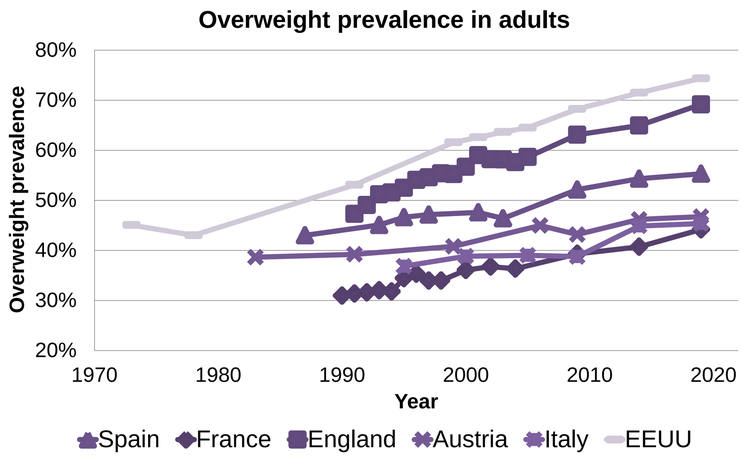

Figure 1. The graphic shows the increasing prevalence of overweight adults in industrialized countries. Spain is predicted to have more than half of the population suffering from overweigh by 2020. *Figure taken from: Foresight.Tackling Obesities: Future Choices – Project report (2014)*

Pharmacological treatment ofobesity aim not only to reduce body weight, but it also to prevent health comorbidities. First step of obesity treatment is using non-pharmacologic method such as nutrition, physical activity, and behaviour therapy. If the patient does not achieve adequate weight loss pharmacotherapy can be considered before applying more invasive interventions such as surgical treatment.

Past anti-obesity therapies

Obesity is found in ancient time, and so do medications to treat it. Moreover most of the last century anti-obesity therapies are now withdraw.

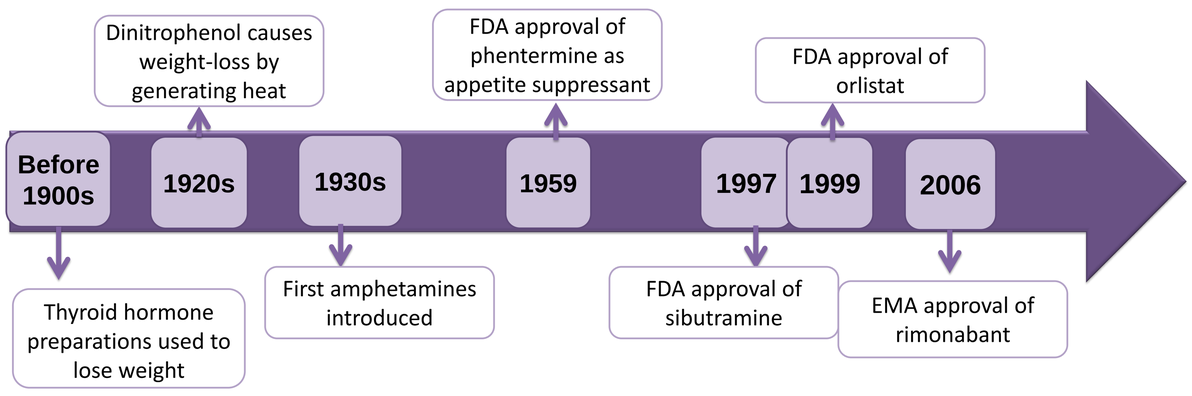

Figure 2. Timeline indicating some of the many anti-obesity therapies used in the past that have been retired from the market due to its side effects. *Modified from: Trends Neurosci.; 2013;36(2):133–40*

Current anti-obesity therapies

Nowadays there are only four drugs available in the market to treat obesity that have the approval of the FDA, whereas in Europe there is only three of them. Moreover, only two of those pharmacological treatments are approved for a long- term therapy (Orlistat and Lorcaserin) whereas the other two (Phenetermine/topiramate and Naltrexone/Bupropion) are only approved for short term management of obesity (≤12 weeks).

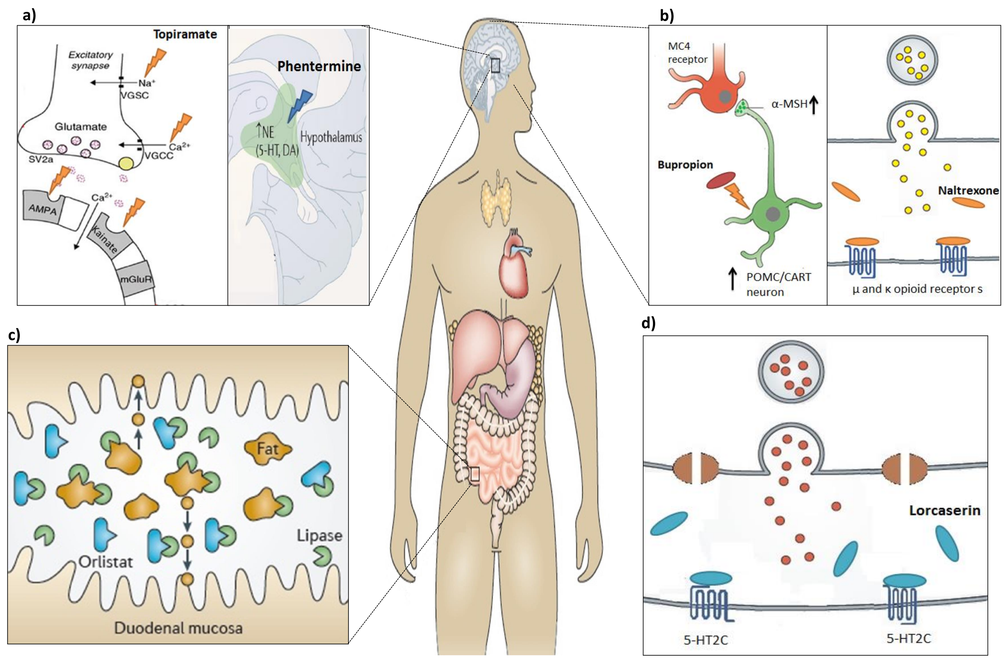

Figure 3.Mechanims of action of the current anti-obesity therapies on the market. **a)** Phentermine increase the adrenergic tone that reduces food intake and increases resting energy expenditure. Topiramate induces appetite suppression and satiety via a combination of (GABA) mediated inhibitory activity, modulation of voltage-gated calcium and sodium channels, kainite glutamate receptors. **b)** Bupropion stimulated hypothalamic proopiomelanocoritn (POMC) neurons that release alpha-melanocyte stimulating hormone (α-MSH) which binds to MC3 and MC4 receptors inhibiting food intake and inducing satiety. Naltrexone long-acting opioid receptor antagonist (mainly of μ and κ receptors that antagonize the effects of β-endorphins **c)** Inhibition of both pancreatic and gastric lipases required for the hydrolysis of fat **d)** Selective and potent agonist of 5-HT2C that induce satiety. *Modified from : Nat Rev Drug Discov 2012;11(9):675–91*

Risks of anti-obesity therapies

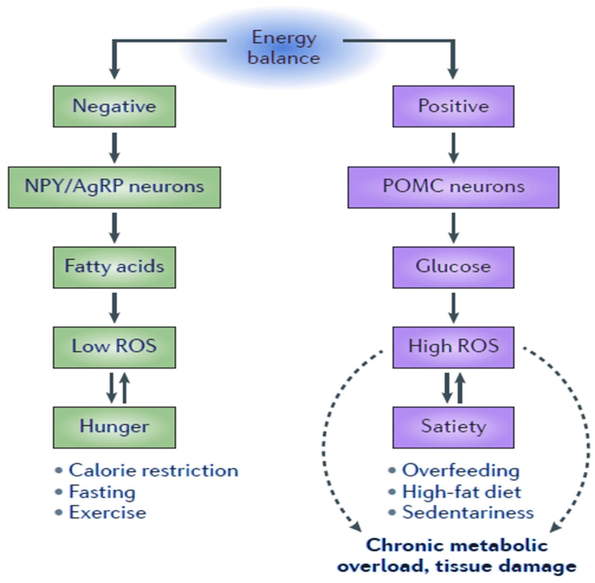

Figure 4. During a positive energy balance, POMC neurons are firing actively using glucose as main fuel at the same time they increased ROS accumulation in these cells. Thus, sustained ROS levels in POMC neurons appear to favour satiety. So, glucose-induced ROS generation in POMC neurons is actually fundamental to the promotion of satiety. *Extracted from: Nat Rev Drug Discov 2012;11(9):675–91*

The activation of POMC neurons, which utilize glucose as a main fuel to promote potential actions, promote of satiety, which leads to suppression of feeding and increases energy expenditure.

On the other hand, NPY/AgRP neurons are known to utilize mainly fatty acids to promote potential actions, promote satiety which leads to food craving.

The by-products of glucose or fatty acids oxidation produce reactive oxygen species (ROS) which plays a critical role in the promotion of POMC neuronal firing.

Satiety relies on continuous ROS production in the hypothalamus and an associated glucose-triggered ROS production in the periphery. That would mean that sustained satiety induced by anti-obesity therapies will , by default, result in ROS-induced damage in central and peripheral tissues.

Future perspectives

Due to the risks of anti-obesity drugs that promote satiety, investigator are now are trying to target other pathways involve in calorie restriction, exercise and also to act on peripheral tissue rather that in the central nervous system to avoid side effects of nowadays therapies.

Calorie restriction

- Promotion of pathways involved in hunger and calorie restriction are related with longer lifespan
- Calorie restriction reduce inflammation and down regulate immune responses which improved several risks factors for chronic diseases.
- **Resveratrol** may act as a calorie restriction mimetic and enhanced health indexes, despite not ameliorating obesity.

Exercise

- Promote pathways involved in the effects of regular exercise to improved the health in these subjects
- **Metformin: inductor** of AMP-activated protein Kinase (AMPK) signalling
- **Irisin:** acts in the white adipose tissue to stimulate the expression of UCP1 and brown-fat development

Peripheral tissue

- Target peripheral tissues such as adipose tissue, as a mean to avoid undesirable side effects on the central nervous system
- Inhibitors of methionine aminopeptidase 2 (MetAP2) like **Fumagilin** inhibits angiogenesis in adipose tissue resulting in a decrease in fat accumulation
- Targeting the brown adipose tissue in order to increase its energy expenditure may be also a future approach

Conclusions

- Mechanisms underlying metabolism homeostatic energy needs to keep being investigate in order to identify new targets and also to have a better comprehension of the pathogenesis of obesity
- Pathway that do not involved in promotion of satiety may offer a solution to the development of new anti-obesity drugs with less side effects
- Meanwhile new anti-obesity drugs are discovered, governments should keep invest in obesity prevention

Bibliography

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