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"ENDOGENOUS OPIOIDS: A STEP TO PREVENT OBESITY"

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The unprecedented number of temptations in our consumer society has created new challenges for obesity research. Constrained food availability no longer exists in most countries of the world, replaced instead by a superfluity of easily accessible and cheap sources of energy. This dramatic alteration in the food environment has substantially affected our normal food intake and exaggerated the physiologic distinction between *homeostatic* hunger—that which follows a period of relatively prolonged food deprivation—and *hedonic* hunger, which occurs in the absence of privation. The latter is largely regulated by the palatability and rewarding properties of food, and is believed to play a critical role in the escalating prevalence of obesity. Obesity and its secondary chronic diseases are a massive burden on the Western healthcare system; therefore the pharmacological industry has taken an interest in the development of weight reducing therapeutics. Recent trends of opioid and cannabinoid systems are implicated in mediating the hedonic value of palatable foods, both opioid and cannabinoid antagonists have been explored for their possible use as anorectic compounds, and both have demonstrated promising results.

Keywords:- Obesity, Opoids

Introduction

Humans eat for many reasons, including the rewarding qualities of foods. A host of neurotransmitters have been shown to influence eating behavior and some of these appear to be involved in reward-induced eating. Endogenous opioid peptides and their receptors were first reported more than 30 years ago, and studies suggesting a role of opioids in the regulation of food intake date back nearly as far. Opioid agonists and antagonists have corresponding stimulatory and inhibitory effects on feeding [3].Obesity has multiple causes, and results from complex interactions between genetic, psychological, socioeconomic, and cultural factors[4].The opioid system consists of three receptors, mu, delta, and kappa, which are activated by endogenous opioid peptides processed from three protein precursors, proopiomelanocortin, proenkephalin, and prodynorphin [5].Opioids produce analgesia by interacting with local opioid receptors in peripheral inflamed tissue [6].

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ENDOGENOUS OPIOID SYSTEM

The endogenous opioid system is one of the most studied innate pain-relieving systems. This system consists of widely scattered neurons that produce three opioids: beta-endorphin, the met- and leu-enkephalins, and the dynorphins [7].

Endorphins: These are endogenous opioids polypeptide compounds.They are produced by the pituitary gland and the hypothalamus in vertebrates during strenuous exercise, excitement, pain and orgasm and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. Endorphins work as "natural pain relievers."

The term "endorphin" implies a pharmacological activity as opposed to a specific chemical formulation. The term endorphin is a general name for many opioid-like proteins. (It consists of two parts: endo and orphin; these are short forms of the words endogenous metersorphine which means "a morphine-like substance which is produced by the human body[8].

Types of Endorphins:

Four types of endorphins are created in the human body. They are named alpha, beta, gamma and sigma endorphins. The four types have different numbers and types of amino acids in their molecules. More endorphins are released in the pituitary gland during

times of pain or stress. Exercise increases the endorphin release too. For the same reason, exercise results in a better mood. Athletes also produce high levels of endorphins. They get a "runners high" when the athlete has done a very hard and strenuous exercise.The term "runners high" has been adopted in refer to feelings that endorphins allow humans to feel a sense of power and control over themselves that allows them to persist with activity for an extended time[9].

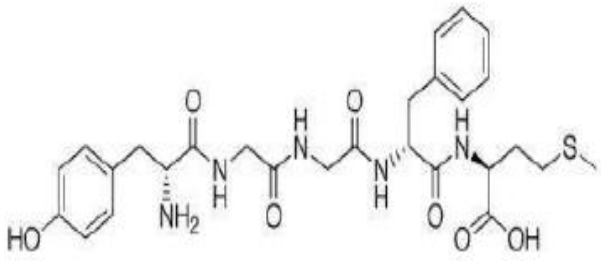
Enkephalins:

Enkephalins are pentapeptides involved in regulating nociception in the body. Discovered in 1975, two forms of enkephalin were revealed, one containing leucine ("leu") and the other containing methionine("met"). Both are products of the proenkephalin gene[8].

- Met-enkephalins has Tyr-Gly-Gly-Phe-Met
- Leu-enkephalins has Tyr-Gly-Gly-Phe-Leu.

Met-enkephalins:

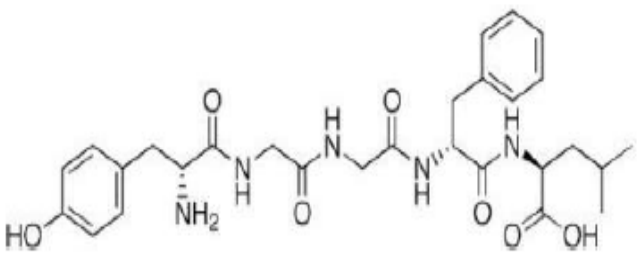
Met-enkephalins are endogenous opioid peptide neurotransmitter found naturally in the brains of many animals, including humans.



Molecular formula: $C_{27}H_{35}N_5O_7S$

Leu-enkephalins:

Leu-enkephalins produce pharmacological effects at both the μ and other opioids receptors. They have much higher selectivity for opioids receptors [10].



Molecular formula: $C_{28}H_{37}N_5O_7$

Dynorphins:

Dynorphins arise from the precursor protein prodynorphin.When prodynorphin is cleaved during processing by proprotein convertase 2 (PC2), multiple active peptides are released: Dynorphins A, Dynorphins B. Dynorphin A, Dynorphin B contains a high proportion of basic amino acid residues, particularly lysine and arginine as well as many hydrophobic residues. Dynorphins are produced in many different parts of the brain, including hypothalamus, hippocampus, midbrain, medulla, pons and the spinal cord and has many different physiological actions, depending upon their site of production.Dynorphin produced in the arcuate nucleus and in orexin neurons of the lateral hypothalamus affects the control of appetite. These large dense-core vesicles differ from small synaptic vesicles in that a more intense and prolonged stimulus is needed to cause the large vesicles to release their contents into the synaptic cleft [11].

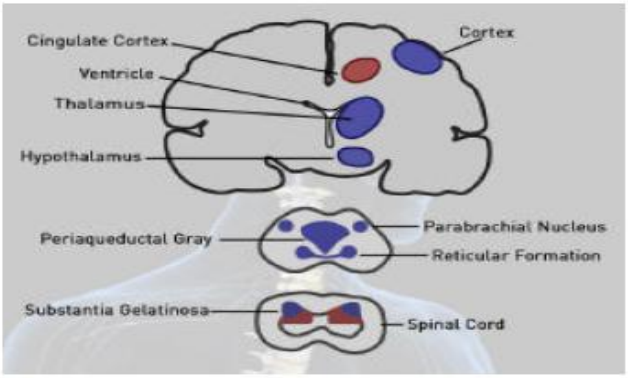


Fig. 1: Major sites of endogenous opioid production and opioid receptors.

Endomorphins:

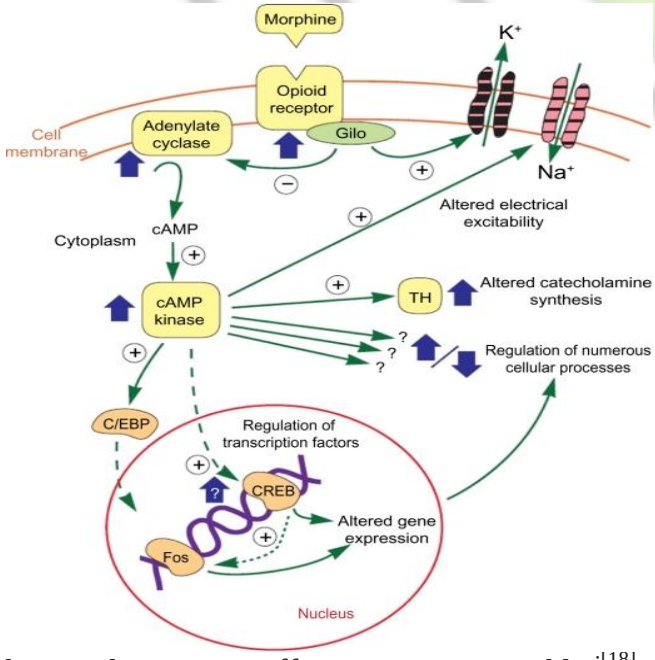
Endomorphins are of two types of tetrapeptides- Endomorphin-1 (Tyr-Pro-Trp-Phe-NH) and Endomorphin-2 (Tyr-Pro-Phe-Phe-NH). Endomorphins have the highest known affinity and specificity for the μ opioid receptor. Endomorphin-1 is widely and densely distributed throughout the brain and upper brainstem and is particularly abundant in the nucleus accumbens (Nac), the cortex, the amygdala, the thalamus, the hypothalamus, the striatum, the dorsal root ganglia, the nucleus of the solitary tract, the periventricular hypothalamus and the dorsomedial hypothalamus, where it is found within histaminergic neurons and may regulate sedative and arousal behaviors. In contrast, Endomorphin-2 is more prevalent in the spinalcord and lower brainstem. They play important role in perception of pain, responses related to stress and complex functions such as reward, arousal and vigilance, as well as autonomic, cognitive, neuroendocrine and limbic homeostasis [12, 13]

OPIOID RECEPTORS:

These opioid receptors are G-linked proteins embedded in the cell membrane. When the opioid attaches to the receptor, the receptor is activated,

releasing a portion of the G protein, which diffuses within the cytoplasm until it reaches its target (either an enzyme or an ion channel). These targets alter protein phosphorylation via inhibition of cyclic AMP (cAMP), which acts as a second messenger within the cell [14].

The term "opioid" is now used broadly to describe any compound that exerts activity at an opioid receptor. The opioid receptors were first discovered in 1972 and the first endogenous opioid (enkephalin) was subsequently discovered in 1975[15]. The different opioid receptors include . *m*orphine (*m*u), *k*etocyclazocine (*k*appa) and vas *d*eferens (*d*elta). Recently, a fourth opioid-like receptor has been included in the opioid receptor family and is termed the nociceptin orphanin FQ peptide receptor. Receptor nomenclature has changed numerous times but current International Union of Pharmacology (IUPHAR) opinion is MOP (mu), KOP (kappa), DOP (delta) and NOP for the nociceptin orphanin FQ peptide receptor[16]. A novel group of peptides has beenEndogenous opioid peptides and their receptors are distributed in the periphery (eg, heart, blood vessels, sympathetic nerves, and adrenal glands) as well as in the central nervous system ,providing the structural bases for numerous interactions in systemic circulatory regulation. Activation of the opioid peptide system in the periphery has been shown to presynaptically inhibit norepinephrine release from sympathetic nerve terminals with subsequent vasodilation. Intravenous administration of dynorphin and ß-endorphin produces hypotension in experimental animals and humans[17].



The opoids receptors affinity are given in table :[18].

Table: Opioid receptors, their location, and response mediated by them

RECEPTOR	CNS LOCATION	RESPONSES ON ACTIVATION
M	Brain (laminae III and IV of the cortex, thalamus periaqueductal gray), spinal cord (substantia gelatinosa)	μ1: supraspinal analgesia, physical dependence; μ2: respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence
K	Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)	Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release
Δ	Brain (pontine nucleus, amygdala, olfactory bulbs, deep cortex)	Analgesia, euphoria, physical dependence

The opioid analgesics most commonly used in clinical practice bind selectively to the μ receptor and are called μ-agonists. Morphine is considered the prototypical μ-agonist. Although there are many similarities between morphine and the other μ-agonists, the different drugs can produce varied effects in the individual patient. For example, when a patient who is chronically exposed to one μ-agonist is switched to another, pain can often be controlled by doses of the second drug that are far lower than predicted by their relative potencies, and both the pattern and severity of nonanalgesic effects can be distinct. This observation, now known as incomplete cross-tolerance,suggests that these μ-agonists are not acting through identical receptors. Pharmacologic studies completed more than a decade ago demonstrated that there were at least 2 μ receptors, which were labeled μ1 and μ2 receptors. After the cloning of the μ receptor, MOR-1, investigators have evaluated the possibility of different alleles in the gene coding for MOR-1 and different phenotypes from these genes based on single nucleotide polymorphisms (so-called splice variants). Studies have confirmed the existence of different alleles in the population, and antisense mapping of gene-coding fragments known as exons has established the existence of multiple polymorphisms[19].

PHARMACOLOGY OF OBESITY

Obesity is well-recognized as a global epidemic and is associated with various co-morbidities, including hypertension, insulin resistance and other components of the metabolic syndrome. Obesity is one of the biggest health threats, for Western society, in the twenty-first century. Obesity is defined as having a

body mass index (BMI; weight, in kilograms, divided by square of height, in meters) greater then 30, whereas overweight is defined as having a BMI over 25. Obesity is a massive burden on the Western healthcare system, because of the increased risk of secondary chronic diseases such as; type 2 diabetes, stroke, cardiovascular diseases, hypertension, gallbladder disease, respiratory problems, sleep apnoea, osteoarthritis and certain types of cancer. Furthermore, obesity also has social and psychological consequences such as depression and low self-esteem. The abundance of 'high calorie food' and sedentary life style in the industrialized countries is perceived as largely responsible for the current epidemic [20].

Epidemiology

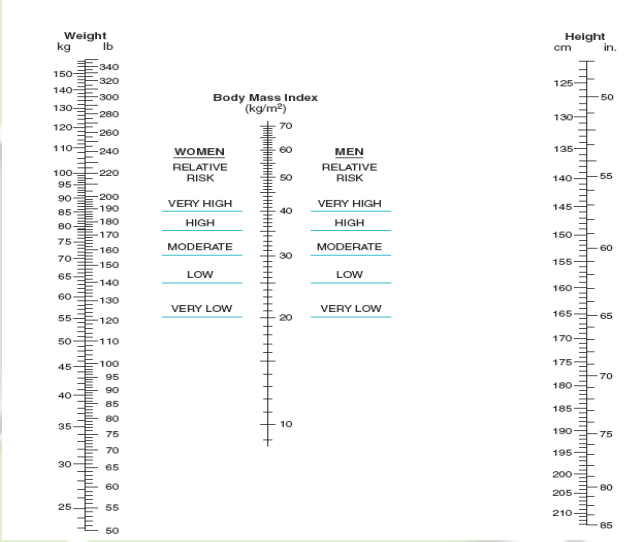
Currently 65% of the US population is overweight and 25% is obese. The prevalence of obesity has increased radically over the previous decade and unfortunately, this development is also seen in various industrialized countries of the world. According to the World Health Organization (WHO), there were 1.6 billion overweight adults and more then 400 million obese adults in 2005 worldwide. The WHO further predicts that by 2015 this number will increase to approximately 2.3 billion overweight adults and at least 700 million will be obese.

Scientific background

Body weight is controlled through a balance between energy expenditure and intake. Energy homeostasis is an intricate process that consists of various interacting homeostatic and non-homeostatic pathways. Homeostatic mechanisms primarily involve the brain, receiving peripheral feedback signals such as hormones, neurons and metabolites, and sending signals to higher brain centres and the autonomic nervous system. It is important to realize that non-homeostatic mechanisms also play a significant role in controlling feeding behaviour. The hedonic aspect of food can initiate feeding, and is unresponsive to the body's homeostatic feedback, therefore uncontrolled feeding can occur. Uncontrolled overfeeding may lead to obesity, therefore anti-obesity drugs are an attractive option. Especially because dieting and exercise to lose weight require a great deal of effort, persistence and willpower, resulting in low compliance in such regimes. The pharmacological industry has therefore taken an interest in the development of weight reducing therapeutics. It has been discovered that the opioid system play a crucial role in the hedonic experience of palatable foods. Since over-consumption of palatable foods is deeply associated with obesity, it is hypothesized that; blocking the function on food intake of the opioid systems might be essential for the pharmacological intervention of obesity [2]

BMI RANGE OR QUETELET'S INDEX:

Another issue relates to the criterion commonly used to define obesity—viz. a BMI >30. Although the prevalence of obesity has doubled over the past few decades, its "morbid" form (BMI >40) has seen an alarming fourfold increase. Consequently, it is not unusual for current research samples to include obese participants with BMIs as high as 60 or 70. By contrast, so-called "normal weight" adults, who are typically used for comparison, comprise the relatively narrow BMI range of 18.5–25. As a result, skewness and heteroscedasticity are highly probable in such case–control studies, and compromise their statistical power.



Nomogram for determining body mass index.

To use this nomogram, place a ruler or other straight edge between the body weight (without clothes) in kilograms or pounds located on the left-hand line and the height (without shoes) in centimeters or inches located on the right-hand line. The body mass index is read from the middle of the scale and is in metric units. The widening BMI range for obesity also suggests this is probably a condition with causally relevant subtypes. It has even been suggested that some cases of obesity be included as a mental disorder in Diagnostic and Statistical Manual of Mental Disorders. It behooves us, therefore, to focus our research efforts on finding biologically based moderator variables that distinguish one form of obesity from another Sturm R. Increases in clinically severe obesity in the United States [21].

ENDOGENOUS OPIOIDS AND TREATMENT OF OBESITY

Opium, derived from the poppy (*Papaver somniferum*), has been utilized as analgesics for centuries. In the 70s, multiple laboratories described animals also synthesize opiate-like substances. These compounds are now known as endogenous opioids. Opioids are synthesized in both the CNS and the periphery and affect a wide range of functions, including: nociception, gastric motility, immune status, cell death, memory hormone secretion, and food intake.

Endogenous opioids bind to a set of receptors that are members of the super-family of G-coupled protein receptors (GCPRs). The distinct receptors are called the μ, Δ and ϰ - opioid receptor, or MOR, DOR and KOR, respectively. The opioid receptors are mostly distributed within the CNS, and are particularly well represented in brain structures associated with food intake [2].

There is much greater agreement about the role of the endogenous opioid system in reward processes, including food intake. The dominant view is that opioids, especially the mu-opioid system, regulate the "hedonics of feeding"—what Berridge calls the "liking"—by their modulation of the palatability of food. These conclusions are largely based on evidence that opioids increase feeding in sated animals more effectively than in those who are food-deprived and that this effect is selective for highly palatable foods. More recent work has identified a major role for mu-opioid receptors, especially in the ventral striatum and amygdala where their activation enhances positive hedonic reactions to sweet and fatty foods.

The mu-opioid receptor (*OPRM1*) gene has been extensively studied for its role in drug abuse, especially for substances like alcohol and heroin. A functional marker—the A118G SNP—has received particular attention. The rarer G118 allele has shown greater affinity for β-endorphin and morphine, but reduced mRNA and protein expression *in vitro*. Although the exact mechanisms remain unclear, *in vivo* evidence supports a "gain-of-function" for those possessing the G allele as seen, for instance, by increased reward from maternal attachment in rhesus macaques infants, increased alcohol stimulation in human subjects, and a greater tendency to drug use and abuse in general. To date, however, we are not aware of any research that has examined *OPRM1* gene in relationship to overeating or weight gain {1}

OPIOIDS IN THE TREATMENT OF OBESITY

Following the promising results of opioid antagonist on weight loss in animals, several controlled trials have been done using oral naltrexone, nalmefene and intravenous naloxone to evaluate their effect on short term food intake in healthy normal weight humans. Sadly, the number of subjects in these tests was limited, ranging from 7 to 26. The results did not show any significant effect on hunger, but one test did show decreased short-term food intake, ranging from 11-29%. And decreased pleasantness of the food was reported in some, but not all of the trials. Nausea is a known side effect of naltrexone, this could possibly be a bias for the decrease in food intake reported. However, around 19% of subjects in the two trials reported nausea after naltrexone treatment, compared to 9% in the placebo group, and the authors conclude that there does not seem to be a direct correlation of reduced feeding and nausea. The effect of naltrexone and naloxone on feeding has also been studied in obese individuals. Again these opioid antagonists were able to decrease short-term feeding behaviour (by about 33%). In some of these trials, a decrease in hunger was reported by participants, and once more there were reports of nausea after opioid antagonist administration. The above mentioned results indicate the opioid antagonists as useful compounds in combating obesity, as they suppress short-term feeding behaviour and are reported to decrease the hedonic value of palatable foods, provided that the negative side-effects can be attenuated. However, there are no published trials demonstrating significant weight loss in obese individuals following opioid antagonist treatment [22].

RECENT DEVELOPMENT IN THE TREATMENT OF OBESITY

Both cannabinoid- and opioid-antagonists are associated with attenuated feeding behaviour in laboratory animals. These compounds have also been tested for their anorectic characteristics in humans.

CANNABINOIDS IN THE TREATMENT OF OBESITY

Following the promising results with cannabinoid antagonists in animals, Sanofi-Aventis started human clinical trials with Rimonabant in the treatment of obesity. The Rimonabant in obesity (RIO) randomised, double-blind, placebo controlled trials included 6600 participants with a BMI > 30kg/m2 or a BMI > 27kg/m2 with obesity-induced disease. At 1-year follow-up, the results of the trials showed a placebo corrected weight loss of 4.7 kg. These results suggested that Rimonabant was a promising anorectic

agent; therefore the European Union licensed it as anti-obesity drug and the National institute for health and clinical excellence approved use in the UK. Sadly, the RIO trials also reported a high incidence of adverse effects; the most common of which were nausea, headache, depression and anxiety. As a result of the psychiatric side effects reported, the US Food and Drug Administration (FDA) refused permission for Rimonabant. In October 2008, Rimonabant was also suspended in the EU. The European Medicines Agency (EMEA) disputed the psychiatric safety due to increased suicide risk and depression.

Rimonabant and Taranabant have a high affinity for the CB1 receptor and function as a full inverse agonist. Therefore, it might be possible to negate some of the negative side effects of Rimonabant using a partial agonist of the CB1 receptor. It has been reported that partial agonists generally have a lower prevalence of adverse side effects then either inverse agonists or antagonists, with a limited reduction of drug efficacy[1].

Potential combined treatment of cannabinoids and opioids in obesity

The physiological mechanisms that regulate body weight are highly complex integrated and redundant, therefore the combined therapy of multiple anorectic agents is postulated to have a greater efficacy than a single obesity agent. And indeed, Rowland and colleagues have convincingly shown that Rimonabant and naloxone together produce a supra-additive anorectic effect. Co-administration with an opioid antagonist not only provides an enlarged efficacy for these two known substances, it also provides a possibility for negating the psychiatric side effects of Rimonabant and other cannabinoid anorectic compounds. Since these two systems seem to synergistically suppress feeding behaviour, lower doses of both opioid and cannabinoid antagonists could be used.

Recently, pruritus has also been confirmed as a significant side effect of CB1 receptor inverse agonists in humans. Tallet and colleagues have shown that in rats this side effect can be attenuated with naloxone treatment. This demonstrates that polytherapy of a CB1 inverse agonist with an opioid antagonist might not only effectively suppress feeding, but also attenuate at least one of the CB1 inverse agonist induced side effects. {2}

CONCLUSION AND DISCUSSION

Obesity is a massive burden on the Western healthcare system, but as of now, an effective pharmacological treatment for this affliction is still missing. Since the opioid and cannabinoid systems are implicated in mediating the hedonic value of palatable foods, both opioid and cannabinoid antagonists have been explored for their possible use as anorectic compounds, and both have demonstrated promising results. Sadly, the scientific interest in cannabinoid antagonists in the treatment of obesity has dissipated because of adverse (psychiatric) side effects.

Multiple groups have indicated that when opioid and cannabinoid antagonists are administered together in animals, they produce a supra-additive anorectic effect. Although, this conclusion is still subject to discussion, it is confirmed that polytherapy of sub-anorectic doses of opioid and CB1 antagonists/ inverse agonists do suppress appetite. Also, recent work has shown that at least one side effect of CB1 inverse agonists can be attenuated by opioid antagonist treatment, thereby further supporting the positive effect of polytherapy. Furthermore, the opioid antagonists used in the aforementioned studies, are all unselective opioid antagonists. Since MORs are primarily associated with feeding behaviour, a μ-selective antagonist could possibly negate some side effects associated with opioid antagonists without losing efficacy. Recent work by Bellocchio and colleagues has shown that the hyperphagic effect of low doses of Δ9-THC is mediated by inhibition of glutamatergic neurotransmission in the ventral striatum. This raises the possibility of cell type-specific heterodimerizations of the CB1, with specific pharmacological characteristics. Future efforts could possibly focus on the development of CB1 antagonists for specific cell types in the ventral striatum, thereby greatly reducing side-effects. Polytherapy of cannabinoid antagonists/ inverse agonists with opioid antagonists could rekindle the scientific interest in the cannabinoid antagonists in the treatment of obesity, however large long-term studies with human test subjects should determine if such combination therapy is effective over a longer duration and if any side effects remain absent. {1, 2, 4}

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