

Fighting obesity and associated risk factors by antagonising cannabinoid type 1 receptors

An article in today's *Lancet* highlights a novel class of drugs aimed at tackling obesity and related metabolic and cardiovascular disorders by selectively antagonising the cannabinoid type 1 receptor (CB₁). Luc Van Gaal and colleagues report the results of a 1-year blinded randomised clinical trial of rimonabant, the first drug of this class, in obese and overweight patients. Rimonabant was reported to cause a pronounced reduction in bodyweight, along with a parallel decrease in waist circumference, and a sustained amelioration of the metabolic profile.

Obesity is no longer a typical, unfortunate outcome of the way of life in the developed world; quite on the contrary, it is now becoming a truly worldwide pandemic.¹ By severely and profoundly influencing the development of type 2 diabetes mellitus, cardiovascular disease, cancer, and gastrointestinal and respiratory disorders, obesity qualifies itself as one of the most serious dangers threatening the developed world.² Olshansky et al³ recently argued that the substantial increase in the prevalence and severity of obesity would have adverse effects on longevity. Consequently, they predicted that the steady rise in life expectancy observed in the modern era would soon come to an end. In a bleak assessment, the authors calculated that, on average, today's young people will live not only less healthy but also shorter lives than their parents did, unless effective population-level intervention is done to reduce obesity on a consistent, regular basis.

Indeed, researchers have emphasised in such a context the crucial and peculiar negative part played by visceral obesity versus subcutaneous fat.⁴ We know that metabolic and cardiovascular diseases aggregate specifically to the abdominal phenotype of obesity.⁴ Visceral adipose tissue is now recognised as an important endocrine gland.⁵ The cloning of the leptin gene paved the way for progressive knowledge that the adipose tissue is a major source of hormones and adipokines, most of which greatly contribute to the development of diseases associated with obesity. Finally, the pivotal role of visceral obesity has been acknowledged by its inclusion in the five clinical features of the metabolic syndrome.⁶

Weight loss, regardless of the way it is achieved, usually diminishes risk factors and alleviates complicating diseases. However, weight loss is often difficult to achieve and patients can become frustrated, particularly when they fail to quickly and effectively meet their expectations. Maintaining weight loss for a long period of time is a difficult task. Changes in lifestyle are hard to adhere to for most patients. Behavioural and cognitive treatments might be useful on an individual basis. However in the long term the results are not encouraging, with most adult patients returning to their pre-treatment baseline within a few years. The few existing approved drugs for treatment of obesity, such as sibutramine and orlistat, achieve only slight weight loss in the short term. This is associated with detectable improvement of metabolic derangements and other cardiovascular risk factors.⁷ On the other hand, available data support

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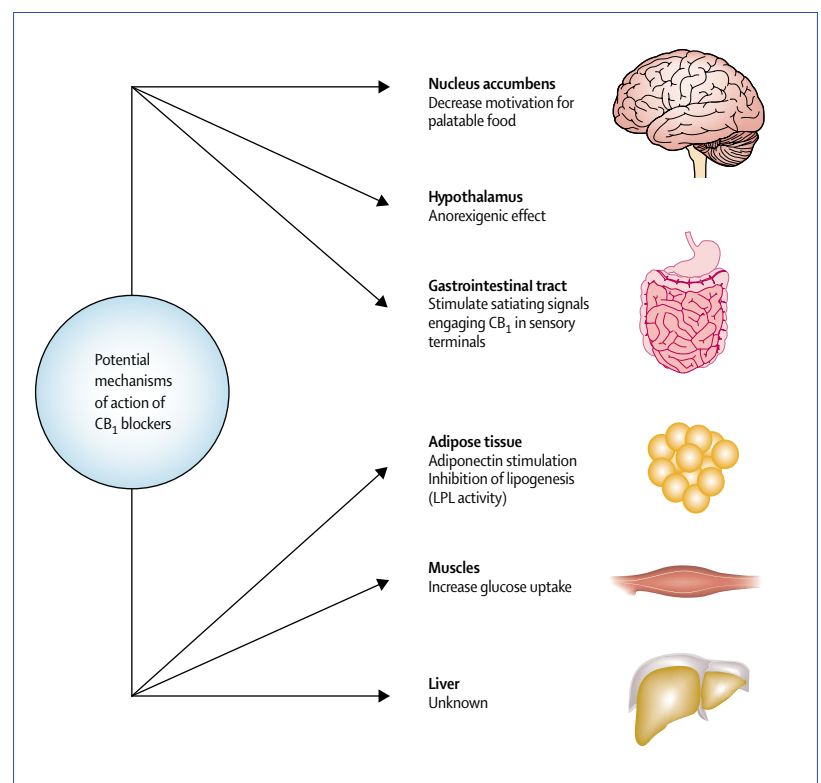


Figure: Potential sites and mechanisms of action of cannabinoid type 1 receptor blockers
LPL=lipoprotein lipase.

the notion that in obese responders, long-term treatment with these drugs may help to maintain weight loss and metabolic benefits for several years.^{8,9} Still unsolved, however, is how to identify responder patients based on genotype and on baseline clinical and biochemical characteristics, which makes adequate management of individuals difficult in the long-term.

The time has come for intensive research on the pharmacotherapy of obesity, in particular the visceral phenotype and the associated metabolic alteration.

Van Gaal and colleagues' report provides substantial advancement on this important topic. A new pharmacological treatment to tackle obesity, and alterations of metabolic and lipid profiles that are often associated, could now be close to clinical practice. The results presented on the use of the CB₁ antagonist rimonabant confirm the crucial role of the endocannabinoid system in the control of food intake and energy balance in humans, as suggested by previous studies in animals.¹⁰ As a result of these animal studies, the endocannabinoid system is known to modulate the rewarding properties of food by acting at specific mesolimbic areas.¹¹ More importantly, the CB₁ receptor and the endocannabinoids (the endogenous ligands of the receptor) have been included as integrated components of the hypothalamic networks controlling appetite and food intake.¹² Novel peripheral mechanisms of action have been attributed to the endocannabinoid system through its ability to directly target adipocytes,^{12,13} gastrointestinal tract¹⁴ and, possibly, skeletal muscles (figure).¹⁵ As expected from studies in rodents,¹⁰ Van Gaal and colleagues' study corroborates the possibility that, in addition to rimonabant's positive effects on weight loss and waist reduction, the drug also has an important and significant weight-independent effect on lipid parameters. Although Van Gaal and colleagues proposed that a rise in adiponectin, a specific protein produced by adipose tissue, might be responsible for these relevant positive changes in lipid profile, other mechanisms could play a part. Full understanding of these yet unknown modes of action is urgently needed to better characterise the ideal phenotype of obese patients to target with CB₁ antagonist drugs. These data, and those from the other ongoing clinical trials with rimonabant, might help us to better tackle obesity and related metabolic and cardiovascular

issues. When additional drugs are available it will also be possible to individually target therapeutic strategies according to phenotype characteristics and to the pathophysiological mechanism of the disease.

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