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Invited review

Prospective therapeutic agents for obesity: Molecular modification approaches of centrally and peripherally acting selective cannabinoid 1 receptor antagonists

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ABSTRACT

Presently, obesity is one of the major health problems in the developed as well as developing countries due to lack of physical work and increasing sedentary life style. Endocannabinoid system (ECS) and especially cannabinoid 1 (CB1) receptor play a key role in energy homeostasis. Food intake and energy storage is enhanced due to the stimulation of ECS hence, inhibition of ECS by blocking CB1 receptors could be a promising approach in the treatment of obesity. Rimonabant, a diaryl pyrazole was the first potent and selective CB1 receptor antagonist that was introduced into the market in 2006 but was withdrawn in 2008 due to its psychiatric side effects. Researchers all over the world are interested to develop peripherally acting potent and selective CB1 receptor antagonists having a better pharmacokinetic profile and therapeutic index. In this development process, pyrazole ring of rimonabant has been replaced by different bioisosteric scaffolds like pyrrole, imidazole, triazole, pyrazoline, pyridine etc. Variations in substituents around the pyrazole ring have also been done. New strategies were also employed for minimizing the psychiatric side effects by making more polar and less lipophilic antagonists/inverse agonists along with neutral antagonists acting peripherally. It has been observed that some of the peripherally acting compounds do not show adverse effects and could be used as potential leads for the further design of selective CB1 receptor antagonists. Chemical modification strategies used for the development of selective CB1 receptor antagonists are discussed here in this review.

1. Introduction

1.1. Obesity

According to World Health Organization (WHO), overweight and obesity are defined as abnormal or excessive fat accumulation in body that may impair health. More than1.4 billion adults in the age of 20 and older were overweight in 2008, among which more than 200 million were men and nearly 300 million women were found to be obese. A very jiggered fact is that more than 40 million children under the age of five were obese in 2011. At present, obesity has become the fifth leading risk factor for global deaths [1]. Obesity creates a major risk factor for a number of diseases like cardiovascular diseases, type 2 diabetes, osteoarthritis, hypertension, stroke, sleep apnea, and certain types of cancers [2,3] indicating that obesity is one of the major challenging health problems these days [4].

1.2. Therapeutic targets for the treatment of obesity

Worldwide, researchers are searching for newer targets for the treatment of obesity. Till date various targets have been identified and unfortunately none have provided a potential therapy for obesity. Hence, there is a worldwide demand to develop a “magic bullet” to lose body weight [5]. For the treatment of obesity, peptide targets like cholecystokinin (CCK-1) agonists, glucagon-like peptide 1 (GLP-1) analogs, amylin analogs, neuropeptide Y agonists, peptide YY agonists, ghrelin antagonists, MCH1 receptor antagonists, MC4 receptor agonists and monoamine targets such as 5-HT_{2B} receptor agonists, 5-HT_6 receptor antagonists, 5-HT_{2C} agonists, β3 AR agonists, dopamine agonists as well as lipase inhibitors, anticonvulsants, cannabinoid 1 (CB1) receptor antagonists, μ-opioid receptor antagonists, sympathomimetic agents, AgRP (agouti-related

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Table 1
Current status of developed anti-obesity drugs with their targets [5–8].

Sr. no	Targets	Drug	Year of approval	Year of withdraw	Current status
A. Agonists					
1.	Sympathomimetic agents	Phentermine	1959		**Approved for short-term use**
2.	Cholecystokinin (CCK-1) agonists	Gl181771X			Phase III
3.	Glucagon-like peptide 1 (GLP-1) analogs	Liraglutide			Phase III
4.	Neuropeptide Y agonists	Obinepitide			Phase II
		Valneperil			Phase II
		TM30339			Phase I
5.	MC4 receptor agonists	MK-0493			Phase II
6.	5-HT_{2B} receptor agonists	Fenfluramine	1973	1997	
		Dexfenfluramine	1996	1997	
7.	5-HT_{2C} receptor agonists	Lorcaserin	**Approved in 2012 on re-filing**		
		ATH-X105			Phase II
8.	β3 AR agonists	LY377604			Phase II
		KRP-204			Phase II
B. Antagonists/inhibitors					
9.	MCH1 receptor antagonists	NGD-4715			Phase II
10.	5-HT_6 receptor antagonists	BVT.74316			Phase I
		PRX-07034			Phase I
11.	Dopamine (D3) antagonists	GSK598809			Phase I
12.	Cannabinoid 1 (CB1) receptor antagonists	Rimonabant	2006	2008	
13.	Neuropeptide Y5 receptor antagonists	S-2367			Abandoned in 2011 (Phase II)
14.	μ-Opioid receptor antagonists	GSK 1521498			Phase I
15.	Sodium glucose transporter-2 (SGLT-2) antagonists	Remogoflozin etabonate (GSK189075)			Abandoned in 2010 (Phase I)
16.	Lipase inhibitor	Orlistat	1999		**Available in market**
		Cetilistat			Phase III
17.	Mitochondrial transfer protein inhibitor	SLx-4090			Abandoned in 2010 (Phase II)
18.	Agouti-related protein (AgRP) inhibitor	TPN435			Phase I
19.	Methionine aminopeptidase ($MetAP_2$) inhibitors	ZGN-433			Phase I
20.	Diacylglyceride acyltransferase ($DGAT_1$) inhibitors	AZD7687			Phase I
		PF-04620110			Phase I
21.	Sodium glucose co-transporter-2 ($SGLT_2$) inhibitors	PF-04971729			Phase I
C. Combination therapy					
22.	Norepinephrine/dopamine releasing stimulators	Diethylpropion	1959		**Approved for short-term use**
		Benzphetamine	1960		**Approved for short-term use**
		Phendimetrazine	1982		**Approved for short-term use**
23.	NA/5-HT reuptake inhibitors	Sibutramine	1997	2010	
24.	Antiepileptic, dopamine/noradrenaline reuptake inhibitor	Empatic (Zonisamide + Bupropion)			Phase III
25.	5-HT/DA/NA reuptake blocker	Tesofensine			Phase III
		DOV21947			Phase II
26.	Sympathomimetic agent, weak carbonic anhydrase inhibitors (exact mechanism for obesity is still unknown)	Quexa (Phentermine + topiramate)	Approved in 2012 on re-filing		
27.	Dopamine and noradrenaline reuptake inhibitors	Contrave (Bupropion + naltrexone)			FDA declined in 2011 and asked for data on long term cardiovascular risk
28.	Amylinomimetic/leptin analog	Pramlintide/metreleptin			Phase II programme terminated in 2011

protein) inhibitors, $MetAP_2$ (methionine aminopeptidase) inhibitors mixed noradrenaline/serotonin reuptake inhibitors, mixed dopamine and noradrenaline reuptake inhibitors and mixed noradrenaline dopamine and serotonin reuptake inhibitors have been identified [6]. Phentermine, a sympathomimetic amine was approved for short-term use by FDA in 1959 as an anti-obesity agent [7]. But phentermine was withdrawn from Europe market due to its risk of cardiovascular effects and abuse potential [6]. Lorcaserin is a selective 5-HT_{2C} receptor agonist. It was initially rejected in 2010 due to carcinogenicity observed in preclinical studies, but on re-filing FDA approved lorcaserin in July 2012. A CB1 receptor antagonist, rimonabant was withdrawn from the market in 2008 due to its psychiatric side effects [8]. Orlistat, a gastrointestinal and pancreatic lipase inhibitor acting peripherally was the first long-term use drug approved by FDA for the treatment of obesity in 1999 and is available in the market. It does not show any clinically significant effects on triglycerides or HDL cholesterol. It exhibited gastrointestinal adverse effects like flatulence, steatorrhoea, malabsorbtion, faecal urgency, faecal incontinence, abdominal pain, upset stomach, dyspepsia and reduced absorption of fat soluble vitamins [9–11]. Researchers have begun to develop combination therapy for the treatment of obesity. This strategy was adopted due to the fact that various mechanisms are involved in food intake modulation. It has also been proposed that more favourable weight loss and a better safety profile can be achieved by using multiple targeting agents [7]. Qnexa is a combination of topiramate (anticonvulsant) and phentermine (amphetamine derivative) which has completed phase III clinical trial although FDA did not approve Qnexa in its current form in 2010. The FDA had asked for its data regarding teratogenicity in 2011, Qnexa was approved in 2012 [7] after ensuring its safety. Contrave, another drug, is a combination of naltrexone (opioid antagonist) and bupropion (antidepressant). FDA's Endocrinologic and Metabolic Drug Advisory Committee voted to support Contrave for approval in 2010. But in 2011, the FDA asked for its data regarding long-term cardiovascular risk assessment [7]. Sibutramine a NA/5-HT