

## Editorial

# Obesity, a health burden of a global nature

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Obesity, the primary health threat in the 21st century, affects the quality of life physiologically, economically and psychologically, irrespective of cultural, financial or ethnic background. Prevalence of obesity has been increasing steadily during the past 30 years worldwide, especially in developed countries. In America, almost one-third of adult population are obese ( $\text{BMI} \geq 30 \text{ kg/m}^2$ )<sup>[1]</sup> and healthcare expenditure for obesity had reached nearly 75 billion USD in 2003<sup>[2]</sup>. A similar picture has been seen in developing countries as well where incidence of obesity is rising at an alarming speed. In China, according to one report, 12.1% and 2.6% of the urban population are either overweight ( $25 \text{ kg/m}^2 \leq \text{BMI} \leq 30 \text{ kg/m}^2$ ) or clinically obese ( $\text{BMI} \geq 30 \text{ kg/m}^2$ )<sup>[3]</sup>. The situation in children is more disturbing: a 2005 study conducted in northern coastal large cities of China shows that the combined prevalence of obesity had reached 32.5% in boys and 17.6% in girls, respectively<sup>[4]</sup>. Possible contributing factors may include steady economic growth, lifestyle changes and significantly reduced family size since the late 1970's.

From a medical stand point, obesity contributes to a broad range of health issues, involving type 2 diabetes mellitus, cardiovascular and kidney diseases (see review by Barton), as well as certain cancers, *etc*<sup>[5]</sup>. It significantly increases mortality, causes physical impairment and psychological stigma, and results in economic burden that is largely unmanageable even in many affluent societies. Therefore, prevention and treatment of obesity are a common challenge with extraordinary urgency to both developed and developing nations, and all-out efforts are required to exploit efficient strategies, from policy to education, from research to industry, and from physicians to patients.

Obesity is generally recognized as disturbances in energy homeostasis between nutrient intake and expenditure. The balance is controlled by the central nervous system (CNS),

mainly the neurons located in hypothalamus. They sense nutrient molecules in circulation and peripheral signaling proteins released by organs in order to regulate energy homeostasis<sup>[6]</sup>. However, the exact molecular mechanisms relative to pathogenesis of obesity remain elusive (see review by Herbst), and may include interaction of different genes (see article by Ke *et al*), environmental factors, life style, social status and even intrauterine or neonatal nutritional states<sup>[7]</sup>. It is believed that a chronic, low grade inflammation, in response to excess nutrients or energy, in the metabolic tissues is involved in the development of obesity (see review by Gao and Ye). A cascade may exist starting from release of inflammatory cytokines [tumor necrosis factor (TNF)- $\alpha$ , interleukin-1(IL-1) $\beta$ , CCL2, *etc*] and activation of inflammatory kinases (JNK, IKK, PKR *etc*) by metabolic cells, progressing towards tissue malfunction (*eg* insulin resistance), and eventually linking inflammation to obesity-related diseases, such as type 2 diabetes<sup>[8]</sup>.

While prevention is largely dependent upon change of life style, therapeutic approaches are dominated by medications that result in weight loss, covering both small molecules and peptides aiming at a variety of drug targets (Tables 1 and 2)<sup>[9–11]</sup>. Of which, sibutramine, phentermine, rimonabant, lorcaserin, contrave, qnexa, liraglutide, tesofensine and velineperit, *etc*, target the CNS and decrease energy intake via reducing appetite or increasing satiety, whereas orlistat and cetilistat interfere with nutrient absorption in the digestive system. Although the pipeline looks prosperous, only one drug (orlistat) is available at present for long-term weight control because sibutramine was withdrawn last year due to an increased cardiovascular risk<sup>[12]</sup>. Others that were approved for short-term treatment (*eg* phentermine, diethylpropion, benzphetamine and phendimetrazine) all have the limitation of controlled use because of potential drug abuse<sup>[13]</sup>.

With worldwide demands for a “magic bullet” to loose body weight, major pharmaceutical companies are chasing after the multibillion-dollar obesity market even under extremely high risks. In 2010, Sanofi-Avantis decided to discontinue all ongoing clinical trials and to suspend sales of its cannabinoid

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**Table 1.** Anti-obesity drugs approved, rejected, withdrawn or revised by the FDA.

Drug	Company	Mechanism of action	Comments
<b>Anti-obesity drugs presently on the market</b>			
Orlistat	Roche, GSK	Pancreatic lipase inhibitor	Approved for long-term use in 1999
Phentermine	Not available	Adrenaline reuptake inhibitor	Schedule IV drug, approved for short-term use
Diethylpropion	Not available	Norepinephrine/dopamine releasing stimulator	Schedule IV drug, approved for short-term use
Benzphetamine	Pharmacia	Norepinephrine/dopamine releasing stimulator	Schedule III drug, approved for short-term use
Phendimetrazine	Not available	Norepinephrine/dopamine releasing stimulator	Schedule III drug, approved for short-term use
<b>Anti-obesity drugs that await for decisions</b>			
Contrave	Orexigen	Bupropion+naltrexone	The FDA requested data on long-term cardiovascular risk assessment in 2011
Qnexa	Vivus	Phentermine+topiramate	The FDA requested data on teratogenic potential in 2010
<b>Anti-obesity drugs rejected by the FDA</b>			
Rimonabant	Sanofi-Aventis	CB1R antagonist	Not approved in the USA due to its psychiatric side-effects and withdrawn from the European market in 2009 for increased risk of serious psychiatric disorders
Lorcaserin	Arena Pharma	Selective 5-HT <sub>2C</sub> receptor agonist	Not approved due to concerns over carcinogenicity observed in rats in 2010
<b>Anti-obesity drugs withdrawn from the market</b>			
Fenfluramine and dexfenfluramine	Wyeth-Ayerst	5-HT <sub>2B</sub> receptor agonist	Withdrawn after reports of valvular heart damage and primary pulmonary hypertension in 1997
Phenylpropranolamine	Not available	Norepinephrine/dopamine releasing stimulator	Withdrawn for increased risk of hemorrhagic stroke in 2000
Sibutramine	Abbott	NA/5-HT reuptake blocker	Withdrawn for increased risk of cardiovascular events in 2010

5-HT, 5-hydroxytryptamine; NA, noradrenaline; CB1R, cannabinoid 1 receptor; FDA, Food and Drug Administration; GSK, GlaxoSmithKline.

**Table 2.** A glance of new anti-obesity drugs in the pipeline.

Drug	Company	Mechanism of action	Stage
Empatic	Orexigen	Bupropion+zonisamide	Phase III
Pramlintide	Amylin	Leptin analog + amylin analog	Phase III
Cetlistat	Alizyme/Takeda	Pancreatic lipase inhibitor	Phase III
Liraglutide	Novo Nordisk	Long-acting GLP-1 analog	Phase III
Tesofensine	NeuroSearch	NA/DA/5-HT reuptake inhibitor	Phase II
Velneperit	Shinogi	Neuropeptide Y5 receptor antagonist	Phase II
Obinopitide	7TM	PPY3-36 and pancreatic polypeptide analog	Phase II
LY377604	Eli Lilly	β-3 adrenergic receptor agonist	Phase II
ZGN-433	Zafgen	MetAP2 inhibitor	Phase I
PF-04971729	Pfizer	SGLT2 inhibitor	Phase I
PF-04620110	Pfizer	DGAT1 inhibitor	Phase I
GSK 598809	GSK	D3 receptor antagonist	Phase I
GSK 1521498	GSK	μ-opioid receptor antagonist	Phase I

GLP-1, glucagon-like peptide-1; PPY3-36, peptide YY3-36; MetAP2, methionyl aminopeptidase 2; SGLT2, sodium glucose co-transporter type 2; DGAT1, diglyceride acyltransferase.

1 receptor (CB1R) blocker, rimonabant, following the recommendation from the European Medicines Agency in response to serious psychiatric side-effects<sup>[14]</sup>. Merck and Pfizer wasted no time to cease the development of their versions of CB1R antagonists, taranabant and CP-945598, respectively, making CB1R as a drug target dubious. Thus, a new strategy to discover selective CB1R blockers that predominantly interact with the receptor in the periphery has been debated<sup>[14]</sup>.

Haunted by the withdrawal of sibutramine and the end of CB1R blockers, the developers of anti-obesity drugs experienced further setbacks. Apart from rejecting regulatory approval of Vivus's combination product qnexa and Arena's locaserin<sup>[15]</sup>, the Food and Drug Administration requested a cardiovascular outcome study for another combination therapy, Orexigen's contrave<sup>[10]</sup>. Obviously, the paramount concern on therapeutics against obesity is safety because it is not a fatal disease and requires long-term management. In comparison with physical exercise and diet control that demand for active participation, the advantage of a safe and efficacious pill is unquestionable albeit it is passive in terms of patient efforts.

The multi-facet actions of the gut hormone, glucagon-like peptide-1 (GLP-1), render it ideal as a target for drug intervention<sup>[16]</sup>. Encouraged by early success with a GLP-1 mimetic, exenatide, in diabetic weight loss<sup>[17]</sup>, liraglutide, a long-acting GLP-1 analog, was shown to reduce body weight in both animal models of obesity (see article by Hansen *et al*) and human clinical studies<sup>[18]</sup>. Similar effects in animal models were also seen with a non-peptidic GLP-1 receptor agonist Boc5<sup>[19]</sup> and one of its analogs (see review by He *et al*).

As demonstrated in the treatment of many other diseases, combination therapy is more effective than a single agent. Of the four such products (qnexa, contrave, empatic and pramlintide), qnexa and contrave were previously approved for other indications. Clinical trials revealed that qnexa (phentermine plus topiramate) and contrave (bupropion plus naltrexone) administration induced a net weight loss of 12.2 kg and 6.2 kg, respectively, compared with a reduction of 4.0 kg or 3.2 kg when phentermine or bupropion was administered alone<sup>[10]</sup>.

Facing such an unprecedented challenge on a global scale, it is far from adequate in terms of novel approaches to obesity management. Clearly, the most important task lies in education that alters social behavior capable of preventing the prevalence of obesity from rising. In this special issue, several topics that relate to obesity etiology, animal models (see review by Nilsson *et al*), therapeutics and clinical implications are covered in order to provide a glance of the latest develop-

ments in this important field.

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