Obesity, a health burden of a global nature

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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[6]. 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[7]. 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)-α, interleukin-1(IL-1)β, CCL2, etc] and activation of inflammatory kinases (JNK, IKK, PKR etc) by metabolic cells, progressing towards tissue malfunction (e.g. insulin resistance), and eventually linking inflammation to obesity-related diseases, such as type 2 diabetes[8].

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)[9–11]. Of which, sibutramine, phentermine, rimonabant, lorcaserin, contrave, qnexa, liraglutide and velneperit, 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looks prosperous, only one drug (orlistat) is available at present for long-term weight control because sibutramine was withdrawn last year due to an increased cardiovascular risk[12]. Others that were approved for short-term treatment (e.g phentermine, diethylpropion, benzphetamine and phendimetrazine) all have the limitation of controlled use because of potential drug abuse[13].

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 Anti-obesity drugs approved, rejected, withdrawn or revised by the FDA.

| Drug                      | Company       | Mechanism of action                     | Comments                                                                 |
|---------------------------|---------------|------------------------------------------|--------------------------------------------------------------------------|
| **Anti-obesity drugs presently on the market** |               |                                          |                                                                          |
| 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                           |
| **Anti-obesity drugs that await for decisions** |               |                                          |                                                                          |
| 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                  |
| **Anti-obesity drugs rejected by the FDA** |               |                                          |                                                                          |
| 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-HT₂c receptor agonist         | Not approved due to concerns over carcinogenicity observed in rats in 2010 |
| **Anti-obesity drugs withdrawn from the market** |               |                                          |                                                                          |
| Fenfluramine and dexfenfluramine | Wyeth-Ayerst | 5-HT₂b receptor agonist                  | Withdrawn after reports of valvular heart damage and primary pulmonary hypertension in 1997 |
| Phenylpropanolamine       | 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 |
| Cetilistat   | 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 |
| Obineptide   | 7TM         | PYY3-36 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; PYY3-36, peptide YY3-36; MetAP2, methionyl aminopeptidase 2; SGLT2, sodium glucose co-transporter type 2; DGAT1, diglyceride acytransferase.
1 receptor (CB1R) blocker, rimonabant, following the recommendation from the European Medicines Agency in response to serious psychiatric side-effects[16]. Merck and Pfizer wasted no time to cease the development of their versions of CB1R antagonists, taraabant 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[14].

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[15], the Food and Drug Administration requested a cardiovascular outcome study for another combination therapy, Orexigen’s contrave[10]. 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[16]. Encouraged by early success with a GLP-1 mimetic, exenatide, in diabetic weight loss[17], 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[18]. Similar effects in animal models were also seen with a non-peptidic GLP-1 receptor agonist Boc5[19] 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[19].

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 developments in this important field.

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