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New targets to treat obesity and the metabolic syndrome

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Abstract

Metabolic syndrome (MetS) is a cluster of associated metabolic traits that collectively confer unsurpassed risk for development of cardiovascular disease (CVD) and type 2 diabetes compared to any single CVD risk factor. Truncal obesity plays an exceptionally critical role among all metabolic traits of the MetS. Consequently, the prevalence of the MetS has steadily increased with the growing epidemics of obesity. Pharmacotherapy has been available for obesity for more than one decade, but with little success in improving the metabolic profiles.

The serotonergic drugs and inhibitors of pancreatic lipases were among the few drugs that were initially approved to treat obesity. At the present time, only the pancreatic lipase inhibitor orlistat is approved for long-term treatment of obesity. New classes of anti-diabetic drugs, including glucagon-like peptide 1 receptor (GLP-1R) agonists and Dipeptidyl-peptidase IV (DPP-IV) inhibitors, are currently being evaluated for their effects on obesity and metabolic traits. The genetic studies of obesity and metabolic syndrome have identified novel molecules acting on the hunger and satiety peptidergic signaling of the gut-hypothalamus axis or the melanocortin system of the brain and are promising targets for future drug development. The goal is to develop drugs that not only treat obesity, but also favorably impact its associated traits.

Keywords

humans; obesity; metabolic syndrome; diabetes; therapeutics; drugs; targets

1. Overview and Definition

Metabolic syndrome is a cluster of interrelated metabolic traits that are linked to development of cardiovascular disease (CVD) and diabetes. The very first descriptions of this syndrome appeared nearly 7 decades ago in observational studies. In 1947 Jean Vague (VAGUE, 1956) reported the association between truncal obesity, diabetes, hypertension and their collective effects on cardiovascular disease risk. The list of linked traits was expanded by Albrinks (Albrink and Meigs, 1965) and Avogaro (Avogaro, 2006) to include

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hypertriglyceridemia and hyperinsulinemia, respectively. These observational studies were soon complemented by large prospective randomized trials that established the association of metabolic syndrome with the risk for type 2 diabetes (Haffner et al., 1990) and cardiovascular events (Pyörälä et al., 1998).

Metabolic syndrome is a heterogeneous disorder with a spectrum of traits that may vary significantly from one affected individual to another and even in affected monozygotic twins (Poulsen et al., 2001). This has led to widespread attempts in devising criteria that can unify the diagnosis. In 2001 the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) developed clinical criteria for metabolic syndrome (Expert Panel on Detection, 2001; National Cholesterol Education Program (NCEP) Expert Panel on Detection, 2002). To meet the criteria, the presence of 3 of the following 5 factors in each subject is required: abdominal obesity (a waist circumference of 102 cm for men and 88 cm for women), elevated triglycerides, reduced high density lipoprotein cholesterol, elevated blood pressure, and impaired fasting glucose. ATP III criteria were later modified by the American Association of Clinical Endocrinologists (AACE). Interestingly, no minimum number for the traits was considered as necessary to qualify for the diagnosis. In addition to the traits specified by ATP III, other factors including polycystic ovary syndrome, hyperuricemia and family history of CVD or type 2 diabetes mellitus were added to assist with the diagnosis (Einhorn et al., 2003).

2. Obesity is central to Metabolic Syndrome

The International Diabetes Foundation (IDF) further modified the ATP III definition by making the presence of abdominal obesity a requirement for diagnosis. Indeed, the predominant underlying risk factor for the syndrome besides insulin resistance (Reaven, 1997) has been shown to be abdominal obesity (Carr et al., 2004; Lemieux et al., 2000; Lemieux et al., 2007; Park et al., 2003). IDF specified lower thresholds for abdominal obesity in Asians (90 cm in men and 80 cm in women) (Grundy et al., 2005). It is noteworthy that body weight tends to increase with increasing age, with a peak between the age of 50–59 years (Harris et al., 1997). Currently, the ATP III criteria are the widely accepted definition for the diagnosis, but the threshold for impaired fasting glucose has been reduced from 110 to 100 mg/dL.

3. Obesity as risk factor for cardiovascular morbidity and mortality

Despite initial controversies, there is growing evidence that the excess body weight increases all cause mortality as well as mortality from cardiovascular disease in adults (Calle et al., 1999; Stevens et al., 1998). Obesity is one of the greatest public health epidemics of the 21st century with about 2 billion adults worldwide currently classified as being overweight or obese. Overweight and obesity are linked to adverse health consequences including cardiovascular disease, type 2 diabetes, and malignant disorders. Strikingly, there is a linear relationship between body mass index (BMI) and mortality from coronary artery disease (CAD), stroke and diabetes (Peeters et al., 2003; Whitlock et al., 2009) that starts from “normal” BMI range (Field et al., 2001). Pathological studies in subjects under age 35 have established strong association between BMI and fatty streaks and atherosclerotic

lesions in the coronary arteries (McGill et al., 2002), and epidemiological studies have shown obesity accounting for roughly 20 percent of the population attributable risk of a first myocardial infarction (Yusuf et al., 2005; Yusuf et al., 2004). Furthermore, BMI inversely correlates with the age of onset of first non-ST-segment elevation myocardial infarction (Madala et al., 2008). It is noteworthy that the use of BMI to define obesity has been controversial, as many insulin resistant individuals such as individuals of South Asian origin have central obesity but normal BMI.

The association between obesity and CAD risk factors, including hypertension, hypercholesterolemia, and diabetes mellitus is fairly established (Abate, 2000; Alpert and Hashimi, 1993; Madala et al., 2008; McGill et al., 2002; Modan et al., 1991; Nguyen et al., 2008). Accordingly, weight loss after bariatric surgery has been shown to reduce the incidence of diabetes, hypertension and hyperlipidemia (Sjöström et al., 1999). The molecular mechanisms that link obesity with cardiovascular disease are only partially understood. Understanding of the mechanisms that regulate body weight and its consequences is critical for development of strategies to prevent the growing obesity epidemic and the discovery of effective therapeutics to treat this condition. Recent advances in molecular human genetics have provided significant insight into understanding the molecular basis of obesity and its link to metabolic risk factor.

4. Genetic causes of obesity

Based on studies of twins, adoptees, and families, genetic factors account for 60 percent of the variation in BMI (Maes et al., 1997). BMI is determined by calorie intake and energy expenditure, which are both influenced by genetic factors. Despite strong evidence for the contribution of family history to development and progression of obesity (Pérusse et al., 2005), scientific progress in identifying the underlying genetic causes of the disease in the general population has been modest. To date more than 30 different genes have been identified that have major effects on its pathogenesis (Benzinou et al., 2008; Farooqi et al., 2000; Meyre et al., 2009). These genetic mutations, however, account for only 10% of obesity in the population. Nevertheless, genetic studies have provided significant insight into pathophysiology of obesity. These findings have underscored the central role of hypothalamus as the key regulator of food intake and energy expenditure and the main sensor of body fat and plasma adipokines.

Adipose tissue leptin provides an important link between the peripheral fat deposit and the hypothalamic proopiomelanocortin (POMC) expressing neurons in the arcuate nucleus (Cowley et al., 2001) and paraventricular nucleus (Heisler et al., 2002). Post-translational processing of POMC generates melanocortin peptides α , β , and γ MSH, which stimulate the melanocortin receptors 3 and 4 (MC4R and MC3R) to generate anorectic response and to reduce the fat deposit (Farooqi, 2008; Farooqi et al., 2003; Farooqi et al., 2000; Farooqi, 2007, 2009; Nogueiras et al., 2007; Yeo et al., 2000). Loss of function mutations in the MC4R gene have been associated with both autosomal dominant and recessive obesity (Farooqi et al., 2000). There have also been case reports of patients with obesity and mutations in POMC (Krude et al., 2003) and MC3R genes (Lee et al., 2002). Leptin also inhibits the orexigenic pathway by exerting inhibition on agouti-related peptide (AGRP) and

neuropeptide Y (NPY) neurons in the arcuate nucleus (Gropp et al., 2005). Mice deficient for leptin (ob/ob) or leptin receptor (db/db) are obese and have insulin resistance (Lee et al., 1996) and hyperinsulinemia (Chen et al., 1996). Paradoxically, however, 20 to 30 fold of physiological leptin levels are required in order to promote weight loss in humans or mice (Campfield et al., 1995). This suggests that the main role of leptin is preventing weight loss and maintenance of a minimum body weight. Except for rare individuals with homozygote mutations in leptin gene, the majority of people with common obesity do not have low leptin levels.

Given that obesity and metabolic syndrome are complex traits caused by combination of genes and gene-environment interaction, the approach in identifying disease genes has been primarily through genetic association studies (Laakso, 2004). Genome-wide association studies have identified a number of common variations in genes that are highly expressed in the hypothalamus and affect energy uptake and expenditure (Church et al., 2010), notably FTO (Frayling et al., 2007) and MC4R genes (Loos et al., 2008), though, they impart small effects on the trait.

5. Clinical Management

The goal for subjects with the metabolic syndrome and obesity is to reduce their risk for atherosclerotic disease and diabetes. Despite significant investigation in development of drugs for obesity and metabolic syndrome, to date, success has been mainly limited to surgical interventions as compared to diet or pharmacotherapy. Diets low in saturated and trans fats, with total fat content of 25% to 35% of calories are often recommended but have modest success in limiting disease due to poor adherence. Endurance exercise stimulates oxidative phosphorylation and mitochondrial size and number, and, together with pharmacotherapy, may help in reducing the risk of metabolic syndrome (Orchard et al., 2005). While lifestyle adjustments such as physical activity, weight reduction, and diet can have dramatic effects at individual level they are insufficient at population levels.

It should be noted that while weight loss is generally believed to be beneficial in terms of risk reduction, studies identify a paradoxical relationship in the elderly where moderate weight gain is protective against mortality (Mattila et al., 1986; Rissanen et al., 1991).

6. Established Medical Therapy for Risk Factor Management in Metabolic Syndrome

There are several fairly well established pharmacotherapies in treatment of metabolic risk factors and prevention of cardiovascular complications. The goal for antihypertensive therapy in patients 60 years old and younger is achieving a blood pressure of <140/90 mm Hg (James et al., 2014). Most data support use of angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for hypertension in subjects with metabolic syndrome and type 2 diabetes mellitus, CAD or chronic kidney disease. One reason for this preference is the adverse effects of most other antihypertensive medications. While diuretics are the most commonly used anti-hypertensive drugs, these may increase the chance of progression to full-blown diabetes mellitus in patients with metabolic syndrome.

Metformin, together with lifestyle intervention has shown to be effective in prevention of diabetes in subjects with impaired fasting glucose (Knowler et al., 2002). Acarbose, alpha-glucosidase inhibitor that reduces postprandial hyperglycemia, has been associated with a significant risk reduction in the development of cardiovascular events, myocardial infarction, and hypertension (Chiasson et al., 2003).

A number of drugs used in treatment of metabolic risk factors have been shown to effectively reduce inflammation measured by plasma CRP levels, including statins, fibrates and thiazolidinediones (TZD). The latter two target nuclear receptors Peroxisome Proliferator-Activated Receptors (PPAR) alpha and gamma, respectively. TZDs improve insulin sensitivity by reducing ectopic fat deposition in the skeletal muscle and redistribution of fat into adipose tissue (Eguchi et al., 2007).

7. Bariatric surgery

Roux-en-Y gastric bypass (RYGBP) or gastric banding are the most effective available therapies for obesity and its comorbidities (Carlsson et al., 2012; Olbers et al., 2012; Sjöström et al., 2007). The mechanisms for efficiency of weight loss are partially understood. There is strong evidence that RYGBP surgery favorably alters the composition of gut hormones (Näslund et al., 1997a; Näslund et al., 1997b). One such gut hormone is PYY that is increased both at baseline and after meal-stimulation in post RYGBP surgery (Korner et al., 2006; le Roux et al., 2006). In rats, ileal transposition alone was sufficient to increase release of anorectic peptides: Glucagon-like peptide-1 and PYY secretion from the transposed segment, resulting in increased circulating PYY levels and reduced body weight (Strader et al., 2005). Accordingly, inhibition of endogenous PYY by using an antiserum in rats that had undergone jejuno-intestinal bypass results in increased food intake (le Roux et al., 2006).

Bariatric surgery has been also associated with reduced mortality (Sjöström et al., 2007). This invasive approach is, however, associated with significant perioperative mortality, surgical complications, frequently requiring redo operations and are reserved for the morbidly obese patients (Mechanick et al., 2009). However, for morbidly obese patients with uncontrolled diabetes, recent studies comparing bariatric surgery to intensive medical therapy have found bariatric surgery to have superior outcomes based on multiple endpoints. At 3 year follow-up, the STAMPEDE (Mingrone et al., 2012) trial reported that only 5% of the medical therapy patients achieved a glycated hemoglobin level of 6% or less compared to 62% of the surgery group. The surgery group similarly had substantially greater weight loss (up to 24.5% vs. 4.2% in the medical therapy group), and improved quality of life scores (Mingrone et al., 2012). Another recent study found similar effects at 6 month follow-up, and additionally suggested that baseline soluble RAGE may serve as a biomarker to predict patients most likely to benefit from the surgical approach (Parikh et al., 2014). Further and more long-term studies will be required to identify optimal candidates for surgery to maximize benefit and minimize risk.

8. Anti-obesity drugs

There are several options for pharmacotherapy for obesity. Use of obesity drugs is approved for patients with a BMI greater than 30, or BMI > 27 when one or more comorbidities such as high blood pressure or type 2 diabetes are present. When combined with lifestyle modifications, drug therapy can generally improve weight loss by 3–5 kg over placebo. While this loss is modest, it may be useful to add pharmacotherapy when patients encounter a plateau in losing weight with lifestyle changes alone. It is important to note, however, that long-term therapy is required, as weight loss attributed to the drug therapy is regained when the drug is discontinued. The new paradigm is that drug therapy is required lifelong, and may be useful for weight maintenance. Tolerance can develop and weight gain occurs even with the continued drug regimen. Intermittent dosing is being explored as a potential strategy to prevent tolerance during long-term treatment.

The earliest drugs that are still in use for obesity belong to amphetamine derivatives like phentermine, desoxyephedrine, and diethylpropion. These drugs are centrally acting sympathomimetics with undesired effects on central nervous system such as agitation, hallucinations, uncontrolled muscle movements, dizziness, difficulty sleeping, irritability, nausea vomiting (Colman, 2005). Tolerance develops rapidly to these agents. As such, these are approved for 12-week treatment only. As increased heart rate can be an adverse effect, therapy with this drug class alone is not optimal for obese patients.

A combination drug Qnexa[®] (phentermine/topiramate ER) was initially rejected by the FDA owing to concerns over historical incidence of oral cleft in offspring of women treated with topiramate for migraine prophylaxis. It was FDA-approved in July 2012 and marketed under the tradename Qsymia[®] (Kiortsis, 2013; Smith et al., 2013). Monthly pregnancy tests are required, and the drug is not recommended for patients with recent or unstable cardiac or cerebrovascular disease due to the potential to increase heart rate. Phentermine/topiramate was not accepted on European market because of long term safety concerns related to cardiovascular complications of phentermine and increased risk for depression/anxiety and cognitive impairment associated with topiramate.

Lorcaserin (Belviq) is an appetite suppressant and weight loss drug with serotonergic properties that was first rejected by the FDA because of concerns about tumor growth in preclinical studies but was finally approved. Drug Enforcement Administration has classified it since 2013 as a Schedule IV drug under the Controlled Substances Act. Because of concerns about tumor growth, risk of psychiatric disorders and valvular disease Arena Pharmaceutical withdrew its marketing authorization application for Lorcaserin in Europe.

Orlistat is a commonly used FDA approved drug for obesity. Orlistat has been also approved by EMEA and is available in Europe. Orlistat inhibits pancreatic lipases, leading to reduced fat uptake by the gut (Borgström, 1988). As it lacks a central effect on appetite and energy expenditure, its effect on weight loss is relatively modest (Li et al., 2005). Nevertheless, it has significant effect on reducing cardiovascular risk, by lowering plasma lipids and glucose, fatty liver disease and systemic blood pressure (Harrison et al., 2004; Torgerson et al., 2004). On the other hand, because it is not centrally acting, it has fewer adverse effects

compared to other obesity drugs. These are mainly gastrointestinal symptoms like dyspepsia, flatulence, abdominal pain and diarrhea, but can be lessened with consumption of a low fat diet (Bray and Ryan, 2007).

9. Withdrawn anti-obesity drugs

The centrally acting serotonin (5-HT)-releasing agents fenfluramine and dexfenfluramine were more potent obesity drugs, which had to be withdrawn from the market due to reports of increased cardiac valvular disease after their use (Teramae et al., 2000). Sibutramine similarly affects the serotonin system and increased heart rate and blood pressure. Sibutramine was withdrawn due to association with increased incidence of cardiovascular events and stroke (Comerma-Steffensen et al., 2014). Rimonabant is a cannabinoid CB1 receptor antagonist/inverse agonist that substantially reduced weight in major clinical trials and was approved in Europe as an anti-obesity agent (Van Gaal et al., 2005). It inhibits the effect of endocannabinoids (e.g. anandamide), which leads to suppression of appetite and weight gain (Kirkham, 2003). Like most other centrally acting drugs, it led to serious psychiatric problems like depression and suicide and had to be withdrawn (Topol et al., 2010). No significant benefit was demonstrated for cardiovascular disorders as the trial was prematurely terminated due to adverse effects (Topol et al., 2010).

10. Anti-obesity drugs in pipeline

Tesofensine (NS2330) is a serotonin–noradrenaline–dopamine reuptake inhibitor from the phenyltropane family of drugs, which is currently under development for therapy of obesity. Tesofensine has completed Phase 1 and 2 trials. It primarily acts as an appetite suppressant, but possibly acts also by increasing resting energy expenditure. The published phase 2 trial showed promising levels of weight loss, greater than those achieved by any other available drugs (Astrup et al., 2008). It is currently in advanced Phase 3 testing, but has recently been under scrutiny for serious side effects (Astrup et al., 2013). The most common side effects include dry mouth, headache, insomnia, and gastrointestinal symptoms, blood pressure and heart rate elevation.

Glucagon-like peptide 1 receptor (GLP-1R) agonists are drugs that are licensed for the treatment of type 2 diabetes. Glucagon-like peptide-1 (GLP-1) is a gut hormone that is secreted by the endocrine L-cells after food intake. It suppresses glucagon production, stimulates pancreatic insulin secretion, prolongs gastric emptying and has been shown to promote satiety (Turton et al., 1996). Since GLP-1 has a short half-life and is degraded by the ubiquitous enzyme dipeptidyl-peptidase IV (DPP-IV), other targets such as DPP-IV inhibitors, DPP-IV-resistant exendin-4 and GLP-1R may be more suitable for clinical development. Large doses of GLP-1R agonist liraglutide can induce satiety in the central nervous system and achieve significant long-term weight loss and improve insulin sensitivity (Astrup et al., 2012; Riddle and Drucker, 2006).

Receptor-interacting protein-140 (RIP140, aka NCOR2) is a nuclear hormone co-repressor, which regulates fat accumulation. It interacts with nuclear receptors such estrogen, thyroid hormone and retinoic acid receptors through 2 C-terminal receptor-interacting domains (RIDs). It serves as a scaffold protein to recruit histone deacetylase complexes and

chromatin-remodeling factors (Cavaillès et al., 1995; Treuter et al., 1998). Mice with global RIP140 knockout are lean and resistant to high-fat diet-induced obesity and fatty liver disease. Silencing RIP 140 in animal models results in a long lasting weight-loss, resistance to diet-induced obesity, and enhanced metabolic rate (Puri et al., 2007; Puri et al., 2008). RNAi against RIP140 is being developed by the CytRx R&D Company for the treatment of obesity and type 2 diabetes.

SMRT is another nuclear hormone receptor co-repressor. Disruption of the molecular interaction between SMRT and nuclear hormone receptors leads to increased adiposity and a decreased metabolic rate in genetically engineered mice (Nofsinger et al., 2008). These studies suggest that targeting the molecular interaction between nuclear hormone receptors and their regulatory cofactors may result in development of novel therapeutics that can control obesity.

Several MC4R agonists have been studied in animal models and humans. A major disadvantage of most MC4R agonists is their poor bioavailability. A piperazine-based highly specific partial MC4R agonist has been shown to have good oral bioavailability in rat (Hong et al., 2011). It reduces food intake by almost 40%. The MC3/4R agonist Melanotan II (MTII) has been similarly shown to cause reduced food intake and weight reduction in rodents, but it is less specific for MC4R, has been mainly administered intracerebroventricularly, and its oral bioavailability is unknown (Getting, 2006). In addition, it exhibits serious side effects such as increased penile erectile activity. The selective MC4R agonist MK-0493 has entered phase 1 and 2 trials, but has shown no significant effect on weight loss (Krishna et al., 2009). Most other MC4R agonists are in the preclinical phase and none are currently available for clinical use.

PPARbeta/delta is emerging as a potential target for the pharmacotherapy of metabolic syndrome. Activation of this nuclear receptor seems improve both insulin sensitivity and plasma lipid profile without causing weight gain (Coll et al., 2009). The limitations in use of TZD drugs include the risk for salt retention and heart failure, and osteoporosis, particularly in elderly women.

Another inhibitor of adipogenesis in preclinical trials is CDDO-Imidazolidine (CDDO-Im). CDDO-Im activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway and results in increased mitochondrial biogenesis, reduced adipogenesis and increased energy metabolism. This drug has been shown to reduce total body weight, and body fat and diminishes hepatic lipid accumulation in rodents (Chartoumpekis and Kensler, 2013).

Novel targets for treatment of obesity

11. Peptidergic signaling pathways

Recent advances in understanding of the peptidergic signaling of hunger and satiety from the gastrointestinal tract mediated by GLP-1, cholecystokinin (CCK), peptide YY (PYY) and ghrelin, and the homeostatic mechanisms of leptin and its upstream pathways in the hypothalamus, have opened new horizons for drug development against obesity (Fig. 1).

12. Ghrelin

Ghrelin is a 28-amino acid peptide with orexigenic effects that is secreted in the gut (Kojima et al., 1999). Its elevated levels were first demonstrated in patients with Prader-Willi syndrome (PWS) (Cummings et al., 2002; Haqq et al., 2003a). Its actions on appetite, food intake and gastrointestinal motility are largely central, in particular by altering signal transduction in the arcuate nucleus of the hypothalamus (Chen et al., 2004). Ghrelin inhibits the activity of POMC neurons by activating neuropeptide Y (NPY) and AgRP.

Ghrelin concentrations in response to a meal are higher in obese compared to normal-weight children (Schellekens et al., 2010). As stated before, ghrelin levels are significantly decreased after RYGBP surgery, while they remain unchanged after diet-induced weight loss (Beckman et al., 2010). This may explain why RYGBP is more effective in achieving long-term weight loss compared to diet alone. Since metabolic syndrome patients and particularly subjects with diabetes are prone to surgical complications, developments of drugs that antagonize ghrelin or GHS-R are of great interest. Octreotide, a somatostatin agonist, has been shown to suppress ghrelin levels (Nørrelund et al., 2002). Its short-term administration in children with PWS suppresses ghrelin levels (Haqq et al., 2003b). Long-acting octreotide has been also shown to decrease acyl and desacyl ghrelin concentrations, however, they have failed to demonstrate significant effects on appetite and body weight (De Waele et al., 2008).

Several GHS-R ligands are in development, and an anti-obesity vaccine which prevents ghrelin from reaching the central nervous system has been developed (Schellekens et al., 2010). Other pharmacologic approaches include antibodies against ghrelin, ghrelin enantiomers which can neutralize ghrelin (Becskei et al., 2008), and decrease acyl ghrelin through inhibition of GOAT (Gualillo et al., 2008). Despite great enthusiasm for development of novel drugs to target ghrelin, most, if not all anti-ghrelin anti-obesity drugs have failed owing to pharmacodynamics problems, but most importantly, lack of sustained effect on weight loss.

13. Peptide YY

The gut hormone peptide YY (PYY) is a 36-amino acid peptide that is synthesized in endocrine L-cells in the distal gastrointestinal tract and is released into the circulation in response to food intake. The peptide has a number of tyrosine residues at the C- and N-terminus and hence, it was named PYY (Tatemoto and Mutt, 1980). Together with neuropeptide Y (NPY) and pancreatic polypeptide (PP), it belongs to a family of peptides, that share a common characteristic U-shape tertiary structure known as the PP-fold (Berglund et al., 2003). These peptides mediate their effects through five subtypes of a 7 transmembrane GPCR known as Y receptor (Y1, Y2, Y4, Y5 and Y6). YY3–36 has the highest affinity for the Y2-receptor subtype, followed by Y1 and Y5 subtypes (Cabrele and Beck-Sickinger, 2000). The activation of presynaptic Y2 receptors by NPY3–36 and PYY3–36 (also NPY and PP) leads to the inhibition of neurotransmitter release (Smith-White et al., 2001). In comparison, Y4 receptors have highest affinity for PP, and modulate its

anorexigenic signaling as well as the vasovagal reflex (Katsuura et al., 2002; Lin et al., 2009).

14. Effects of peripheral PYY administration on feeding

PYY levels are low in the fasting state, but peak after a meal and remain elevated for several hours (Adrian et al., 1985). Peripheral infusion of YY3–36 has dose-dependent anorectic effects in rodents (Batterham et al., 2003; Karra and Batterham, 2010) (Batterham et al., 2002). Peripheral infusion of PYY1–36 has weaker anorectic effects that likely result from its conversion to PYY3–36 by DP-IV (Chelikani et al., 2004; Unniappan et al., 2006). Mice with global PYY knockout are hyperphagic, exhibit weight gain and have increased subcutaneous and visceral fat that are rescued by exogenous replacement of PYY3–36 (Batterham et al., 2006). Unfortunately, PYY1–36 has failed to show inhibitory effects on food intake in humans (Sloth et al., 2007). DP-IV inhibitors currently used in treatment of patients with type 2 diabetes may have mild anorectic effects by increasing the circulating levels of PYY3–36 (Unniappan et al., 2006). They regulate proliferation and differentiations of adipocytes (Kuo et al., 2007).

J-104870 is a selective inhibitor of PYY. It has high affinity for the Y1 receptor and inhibits NPY-dependent calcium influx (Kanatani et al., 1999). Intracerebroventricular and intraperitoneal administration of J-104870 reduces food intake in rats (Kanatani et al., 1999). J-104870 crosses the blood-brain barrier and its intraperitoneal injection increases the drug concentration in the brain (Kanatani et al., 1999). Long-term oral administration of PYY antagonists also led to reduced food intake in obese fa/fa Zucker rats, albeit only a transiently (Raasmaja et al., 2013). Others have shown that high dose systemic PYY antagonists reduce body weight, while low doses reduce adipocyte hypertrophy without effects on plasma lipids, glucose, insulin, and total body weight (Ishihara et al., 2002).

15. NPY receptors as potential targets for anti-obesity drug development

In contrast to PYY, the related 36 amino acid neuropeptide Y (NPY) is mainly expressed in the brain, and mainly activates Y1 receptors, which results in inhibition of adenylate cyclase and cyclic AMP generation, exerting orexigenic effects (Herzog et al., 1992; Motulsky and Michel, 1988; Zhu et al., 1992). Surprisingly, NPY deletion alone does not significantly reduce feeding and body weight in mice (Patel et al., 2006). However, ob/ob mice deficient for NPY are less obese and less severely affected by diabetes (Erickson et al., 1996). This finding has led to the postulation that the major role of neuromodulators is maintaining a minimum body weight as opposed to adjusting body weight. The Y1 receptor mediates the stimulatory effect of NPY, and its long-term administration in mice leads to significant increase in total body weight and total fat accumulation without hyperphagia (Henry et al., 2005). Consistent with its peripheral effects, it promotes rat 3T3-L1 pre-adipocyte proliferation in vitro (Yang et al., 2008). Pharmacological inhibition of the Y1 receptor by central administration of the Y1 antagonists, however, results in significant attenuation of feeding in rodents, suggesting both central and peripheral effects (Kask et al., 1998). Interestingly, Y1 receptor polymorphism in the noncoding region of the gene has been

associated with lower fasting plasma TG and higher plasma HDL concentrations (Blumenthal et al., 2002).

16. Wnt and low-density lipoprotein receptor-related protein 6 (LRP6)

Wnt signaling is an ancient pathway involved in embryonic development. It is also a nutrient sensing pathway, which can be activated by sensing glucose and via insulin signaling (Anagnostou and Shepherd, 2008). Altered function of Wnt/LRP6 signaling has been associated with diabetes and metabolic syndrome (Go et al., 2014; Saxena et al., 2006; Singh et al., 2013a; Singh et al., 2013b). There are 19 different ligands, which can activate canonical as well as non-canonical pathways to regulate transcription, calcium signaling, and cell polarity.

The canonical Wnt signaling pathway consists of cascade of events initiated by binding of a Wnt-protein ligand to a Frizzled family receptor and phosphorylation of its co-receptors LRP5/6. This leads to inactivation of GSK3 β , breakdown of Axin, Dishevelled, and APC complex and subsequent stabilization of β Catenin, which then translocates to the nucleus, where it interacts with TCF/LEF family of transcription activators to promote gene expression (Bilic et al., 2007). GSK3 β is also inhibited by insulin and mediates the cross-talk between insulin- and leptin-signaling pathways. The non-canonical Wnt signaling consists of diverse pathways that conceptually act antagonistically to the canonical Wnt signaling. The non-canonical pathway uses other co-receptors such as ROR2 and is inhibited by phosphorylated LRP6. Noncanonical Wnt signaling activates a Ca^{2+} -CAMKII-NLK (NLK, Nemo like kinase) axis, as well as JNK and p38. Studies suggest that both canonical and non-canonical Wnt are involved in inhibiting the commitment of mesenchymal stem cells toward adipogenic differentiation. This occurs, in part, through regulation of the critical adipocyte transcription factor PPAR γ (Takada et al., 2009). Canonical Wnt/beta-catenin signaling promotes the expression of COUP-TFII, which recruits the SMRT corepressor complex to the first intron of PPAR γ -1, and -2 introns mRNAs (Okamura et al., 2009) (Fig 2), resulting in reduced chromatin acetylation and repression of the PPAR γ gene (Okamura et al., 2009). PPAR γ activation is also repressed in trans by the Wnt5a-mediated non-canonical activation of the CaMKII-NLK cascade, which inhibits adipogenesis in favor of osteogenesis through activation of the histone lysine methyltransferase SETDB (Takada et al., 2007).

Wnt signaling is also involved in central regulation of food intake and body weight. It has been shown that obesity increases hypothalamic GSK3 β activity and its targeted overexpression in mediobasal hypothalamus promotes food intake, obesity, and impaired glucose tolerance (Benzler et al., 2012), while leptin increases its phosphorylation, reducing its activity (Benzler et al., 2013). The mRNAs of Wnt ligands and the Wnt target genes Axin-2 and Cylin-D1 and the phosphorylated LRP6 are down-regulated in the neuropeptide Y neurons of arcuate nucleus of leptin-deficient mice and can be normalized with Leptin treatment (Benzler et al., 2013). Presently, there is no Wnt antagonist in pipeline for treatment of obesity, and paradoxically, the GSK3 β antagonist lithium causes weight gain (Garland et al., 1988). Metreleptin (Myalept), a synthetic analog of the hormone leptin, may be helpful in treating diabetes hyperlipidemia and obesity in patients with impaired Wnt

signaling. It has been approved in the United States as replacement therapy to treat leptin deficiency and lipodystrophy. The drug is also being currently investigated for the treatment of type 1 diabetes in a combined effort led by Juvenile Diabetes Research Foundation, in collaboration with Amylin Pharmaceuticals and the University of Texas Southwestern Medical Center, to improve metabolism and control appetite.

17. Dyrk1 family of proteins-novel targets for drug development

The dual specificity tyrosine-regulated kinases (Dyrk) family of proteins belongs to the larger group of kinases that also includes CDKs, GSK3, and MAPKs (Lee et al., 2000; Tejedor et al., 1995; Yang et al., 2001). Members of the Dyrk family of protein kinases, many of which have been implicated in nutrient sensing, have significant homology in the kinase domain and an upstream sequence called the Dyrk homology domain (Aranda et al., 2011). The Dyrk1B orthologue in yeast, YAK1, is a nutrient sensing protein that is inhibited by glucose. It enhances gluconeogenesis and diminishes glycolysis by inhibiting the yeast transcription factor MSN2 (Livas et al., 2011; Thevelein and de Winder, 1999). Interestingly, EGR1, the mammalian orthologue of MSN2 is induced by glucose in pancreatic β cells (Josefsen et al., 1999) and plays a critical role in regulating insulin biosynthesis, glucose homeostasis, and islet size (Müller et al., 2012), and its deficiency causes reduced insulin synthesis. Dyrk1A is in the critical region of Down syndrome and its excess dose has been linked to diabetes and obesity in Down syndrome patients (Oegema et al., 2010). Dyrk kinases also act as a priming kinases for GSK3B phosphorylation of NFATs, a group of transcription factors that contribute to skeletal muscle development and its glucose and insulin homeostasis and to pancreatic function (Gwack et al., 2006). The Dyrk1B protein is transcriptionally regulated by the Rho GTPases and is ubiquitously expressed (Leder et al., 2003; Leder et al., 1999). It contains different motifs which include a nuclear localization signal (NLS), a kinase-like domain that harbors the NLS, a DYRK-homology box, an N-terminal autophosphorylation accessory region and kinase domain, and the PEST sequence that acts as a signal peptide for protein degradation. Cellular activity of Dyrk proteins is regulated by autophosphorylation, protein stability (via the PEST sequence), and subcellular localization (42).

Dyrk1A and its drosophila ortholog minibrain (mnb) regulate NPY and sNPF (the drosophila functional homolog of NPY) signaling in mice and drosophila, respectively. In mouse hypothalamic cells and drosophila neurons, NPY and sNPF increase the expression of Dyrk1A and mnb by activating the PKA-CREB pathway. Dyrk1A phosphorylation of Sirt1 results in increased Sirt1-dependent deacetylation and activation of the transcription factor FOXO. FOXO further potentiates sNPF/NPY expression and promotes food intake, effects which are neutralized by activation of insulin signaling. Dyrk1A overexpression in mice results in lower FOXO acetylation and increased NPY expression in the hypothalamus, resulting in increased food (Fig. 3).

18. Dyrk1B, a novel gene for truncal obesity, metabolic syndrome

We recently identified Dyrk1B as the disease gene in outlier families with early onset CAD and central obesity in Southwest Iran (Keramati et al., 2014). The Dyrk1B mutation R102C

increased adipogenic transformation of preadipocytes even in the absence of an adipogenic cocktail. The mutant also potentiates the effect of the wildtype Dyrk1B protein on transcription of the rate limiting gluconeogenic enzyme glucose-6-phosphatase (G6pase) in heterozygotes and hence, acts as a gain of function mutation.

Dyrk1B protein is a dual specificity kinase, with its tyrosine phosphorylation activity primarily involved in autophosphorylation, and an arginine-directed serine/threonine kinase activity. Its kinase activities are promoted by signaling from Rho-Rac1 (Deng et al., 2003). Its expression is inhibited by RAS-MEK-ERK (Deng et al., 2003). Interestingly, loss of function mutations in this pathway were recently linked to obesity and insulin resistance in humans and mice (Costanzo-Garvey et al., 2009; Laura R. Pearce, 2013; Revelli et al., 2011). Targets for its serine/threonine phosphorylation include HNF1- α , glycogen synthase (Skurat and Dietrich, 2004), FOXO1 and SIRT1/2 (Guo et al., 2010; Lim et al., 2002), which are all proteins involved in glucose metabolism and transcription of insulin, GLUT2, glucokinase (Al-Quobaili and Montenarh, 2008; Khoo et al., 2003), and Glucose 6-phosphatase (von Groote-Bidlingmaier et al., 2003). Dyrk1B is a pancellular protein (Leder et al., 1999). In malignant cell lines, it has been mainly localized to the nucleus, but is localized in the cytoplasm in human skeletal muscle cells (Friedman, 2007). Thus, its function in malignant cells cannot be automatically assumed for normal cells. It has been suggested that it acts as a cell cycle regulator in the nucleus, primarily by increasing the turnover of p27^{kip} (CDKN1B) (Ewton et al., 2003). Interestingly, mice deficient for p27^{kip} develop atherosclerosis (Naaz et al., 2004), obesity and insulin resistance (Naaz et al., 2004), and mice overexpressing p27^{kip} are protected against atherosclerosis. In the cytosol, Dyrk1B may act as an anti-apoptotic factor by stabilizing p21^{cip} (Gao et al., 2009; Mercer et al., 2005; Mercer et al., 2006).

19. Interplay between leptin, NPY1 and Dyrk family of proteins

Mnb and Dyrk1A and B are highly expressed in arcuate nucleus, olfactory bulb and hippocampus. Both Dyrk1A and B have CREB binding motifs in their promoters. Thus, the stimulatory effects of NPY can similarly affect Dyrk1B expression and FOXO1 activation. These findings suggest a potential role of Dyrk1B in regulation of appetite. Whether Dyrk1B mutation and/or overexpression enhances food intake and weight gain is being currently investigated.

In summary, genetic studies of obesity and adipogenesis in human and rodents over last decade have led to identification of novel genes and pathways that are potentially strong targets for development of novel therapeutics against morbid obesity. The focus of future studies should be focused on targeting genes that constrain ectopic fat generation and prevent its complications.

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Fig. 1.
Schematic of Peptidergic pathways in interplay between gut, adipose tissue hormones and central nervous system regulation of appetite

Fig. 2.
Schematic of canonical and non-canonical Wnt regulation of PPARGgamma (PPARG) transcription in adipogenesis

Fig. 3.

Schematic of interplay between leptin, ghrelin, NPY and Dyrk1A (and possibly B) in central regulation of FOXO1 and food intake. The effects of R102C mutation on these pathways are shown in red.