European Journal of Pharmacology 763 (2015) 64–74

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

New targets to treat obesity and the metabolic syndrome

Kathleen A. Martin [a], Mitra V. Mani [b], Arya Mani [a,c,*]

[a] Department of Internal Medicine, Yale University School of Medicine, USA
[b] Cornell University, USA
[c] Department of Genetics, Yale University School of Medicine, USA

ARTICLE INFO

Article history:
Received 17 November 2014
Received in revised form
19 March 2015
Accepted 30 March 2015
Available online 19 May 2015

Keywords:
Humans
Obesity
Metabolic syndrome
Diabetes
Therapeutics
Drugs
Targets

ABSTRACT

Metabolic syndrome (MetS) is a cluster ofassociated 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 epidemic 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.

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 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 Albrink and Meigs (1965) and Avogaro (2006) to include 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 $\geq$102 cm for men and $\geq$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 ATPIII, 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

* Corresponding author at: Department of Internal Medicine, Yale University School of Medicine, USA.
E-mail address: arya.mani@yale.edu (A. Mani).

http://dx.doi.org/10.1016/j.ejphar.2015.03.093
0014-2999/

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 ($\geq$ 90 cm in men and $\geq$ 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, 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% 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 γMSH, 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, 2000; Farooqi, 2007, 2009; Nogueiras et al., 2007; Yeo et al., 2000). Loss of function mutations in the *MC4R* gene has 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 the 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).