

## ***Homo obesus*: A Metabotrophin-Deficient Species. Pharmacology and Nutrition Insight**

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**Abstract:** In most countries the prevalence of obesity now exceeds 15%, the figure used by the World Health Organization to define the critical threshold for intervention in nutritional epidemics. Here we describe *Homo obesus* (man the obese) as a recent phenotypic expression of *Homo sapiens*. Specifically, we classified *Homo obesus* as a species deficient of metabotrophic factors (metabotrophins), including endogenous proteins, which play essential role in the maintenance of glucose, lipid, energy and vascular homeostasis, and also improve metabolism-related processes such as inflammation and wound healing. Here we propose that pharmaceuticals, nutraceuticals and xenohormetics targeting transcriptional, secretory and/or signaling pathways of metabotrophins, particularly adiponectin, nerve growth factor, brain-derived neurotrophic factor, interleukin-10, and sirtuins, might be new tools for therapy of *Homo obesus*. Brief comment is also given to (i) exogenous metabotrophic agents represented by various classes of drugs, and (ii) adiponutrigenomics of lifespan.

**Key words:** Metabotrophins, metabotrophin-targeted pharmacology.

**When someone declared that life is an evil,  
Diogenes said: Not life itself, but living ill.**

### INTRODUCTION

Obesity is one of the greatest public health challenges of the 21st century. Obesity is already responsible for 2-8% of health costs and 10-13% of deaths in different parts of the world. At its core, obesity is a multifactorial, low-grade chronic inflammatory illness of energy balance, bodyweight being steady when energy is balanced. Morbid energy balance is when the amount of energy consumed as food and drink exceeds the energy used. For instance, an adult on average consumption of 20 kcal a day more than she/he expends, leading to an average weight gain of 1 kg a year, whereas eating 100 kcal a day more than expending, gain up to 5 kg a year [1]. In effect, any intervention that changes such a morbid energy balance may be effective in the prevention and therapy of obesity and related cardiometabolic diseases (CMD) such as atherosclerosis, hypertension, type 2 diabetes mellitus, and metabolic syndrome.

Here we focus on (i) *Homo obesus* as a metabotrophin-deficient species, (ii) metabotrophin-targeted pharmacology, and (iii) adiponutrigenomics of lifespan.

### **HOMO OBESUS: A METABOTROPHIN-DEFICIENT SPECIES**

In analogy to Rita Levi-Montalcini's terminology for neurotrophic factors and neurotrophins [reviewed in 2], the terms "metabotrophic factors (metabotrophins)" are coined for a group of endogenous proteins, which play essential role in the maintenance of glucose, lipid, energy and vascular homeostasis, and also improve metabolism-related processes such as inflammation and wound healing [3,4].

Man the obese, herein dubbed *Homo obesus*, is at high risk of multiple health problems and needs full medical management. In the last 30-40 years, *Homo obesus*, like Diogenes (c. 403-323 B.C.), increasingly says "I am a citizen of the world", thus pointing to the global nature of obesity. Recent studies provide evidence that morbid obesity is a major evil of human health, because plays a pivotal role in the development of CMD as well as nonalcoholic steatohepatitis, obstructive sleep apnea syndrome, polycystic ovary syndrome [1-15] and Alzheimer's disease [16,17]. Specifically, *Homo*

*obesus* is herein described as a metabotrophin-deficient species; a selected list of metabotrophic factors is presented in Table 1. Whether the Israeli sand rat *Psammomys obesus*, a well-known animal model of obesity, type 2 diabetes and metabolic syndrome, is, like *Homo obesus*, a metabotrophin-deficient species remains to be studied.

**Table 1. Endogenous Metabotrophic Factors**

<p><b>Secretory proteins</b></p> <p>Adiponectin [5,9,10,28,42]            NGF [2-7,12,18]            BDNF [2,18-21,41,47-49]            Angiopoietin-like protein 4 [13],            IL-10, IL-1 receptor antagonist*            Ciliary neurotrophic factor*            Glial cell line-derived neurotrophic factor*            Bone morphogenetic protein-9*            Leukemia inhibitory factor*            Metallothionein-I, -II*            Incretins (glucagon-like protein-1, glucose-dependent insulinotropic protein) [26,27]</p>
<p><b>Intracellular proteins</b></p> <p>Sirtuins [33-39]            Peroxisome proliferator-activated receptor-gamma [42]            Aquaporin-7 (AQP7)**, AQP9** [44-46]            Glucose transporters [50]            Uncoupling proteins [51,52]</p>

\* See [2-4 and references therein].

\*\* Discovered firstly by Gheorghe Benga as a water channel protein of plasma membrane of erythrocytes [reviewed in 44], this family of proteins includes today 13 members, AQP-7 and AQP9 being aquaglyceroporins in adipocytes and hepatocytes, respectively. AQP7 gene knockout mice develop insulin resistance and obesity. Both AQP7 and AQP9 may be new pharmacological targets in obesity and related diseases [45,46].

### **METABOTROPHIN-TARGETED PHARMACOLOGY**

#### **Endogenous Metabotrophic Factors**

According to current paradigms, obesity and related CMD are associated with elevated systemic and/or local levels of proinflammatory and thrombogenic mediators, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), hypoxia inducible factor-1 $\alpha$ , interleukin-1 (IL-1),

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