Research on Obesity Caused by Genetic Defects in Specific Populations

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Abstract: Obesity is caused by several factors, including diet, exercise, and the environment. However, one critical factor that many people ignore is genetic abnormality. People are aware of the fact that the amount of food ingested, and the amount of energy exerted can impact the formation of fat. Thus, obesity can be induced by mutations or diseases in genes involved in these three systems in our body. And it is necessary to study the problem of obesity caused by genetic defects. This paper focuses on 5 genetic problems to find the obesity problems and solutions caused by genetic variants. It is found that Leptin and MC4R genes can increase appetite and lead to obesity. And UCP and beta-adrenergic receptor during energy expenditure may result in reduced energy expenditure or hormonal instability in the body, both of which will contribute to obesity. The PPARy gene is essential for fat storage, and a mutation in the gene can result in an inability to store fat, which will eventually lead to significant bodily damage. By studying and compiling the literature, this research has identified the problems that arise after each genetic variation and the corresponding solutions.

1 INTRODUCTION

Genetic defects and obesity have received much attention in the study of genes and metabolism in different populations. Therefore, this paper investigates the causes and solutions of obesity in people with different congenital genetic defects. Many genes have been discussed separately in the context of congenital genetic defects which cause obesity. But there was no definite study. This paper focuses on the category and the study of the obesity problem caused by genetic defects and divides the basic elements of fat production in humans into three major categories. The three categories are food intake, energy expenditure, and fat storage. In each section, one or two genetic defects were found to demonstrate that congenital defects in genes cause obesity.

Meanwhile, this study summarizes and lists the possible obesity problems and solutions separately, demonstrating the root cause for understanding the common genetic defects that cause obesity problems. Therefore, this paper systematically summarizes the essential congenital genes that cause obesity through clinical cases and mouse experiments and provides solutions to the genetic defects as well as future therapeutic prospects. Also, this study will make it easier and more straightforward for researchers in the field of genetic variants and congenital genetic defects to understand the problems.

2 FACTORS THAT INFLUENCE OBESITY

Table 1 lists the five genes that are crucial in obesity, as well as the function of each gene. The function of genes and genetic defect problems will be explored in the following section.

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Table 1: Gene with CLEARLY defined role in obesity (Gao 2014)

GENE WITH CLEARLY DEFINED ROLE IN OBESITY	
GENE NAME	Function
FOOD INTAKE	
LEPTIN	Regulation eating behavior
MELANOCORTIN 4 RECEPTOR	Receptors of neuropeptides
ENERGY EXPENDITURE	
UNCOUPING PROTEIN 1	Proton transporter and thermogenesis
BETA 3 ADRENERGIC RECEPTOR	Lipolysis and thermogenesis in adipose tissue
FAT SYNTHESIS AN STORAGE	
PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMA	Master gene of lipogenesis and adipogenesis

2.1 Genetic Defect Problems

2.1.1 Food Intake Leptin

Food intake usually depends on our appetite and satiety; many genes control appetite and satiety, the first and foremost being the leptin gene. Adipocytes generate the hormone leptin, and leptin is the crucial factor for regulates food intake and energy balance. (Chen 2005) The leptin receptor is a protein that leptin binds to and activates. The leptin receptor protein is located on the cell surface of numerous organs and tissues in the body, including the hypothalamus which is a component of the brain. The primary role of the hypothalamus is to control hunger and thirst and also to control the quality of sleep and mood. In the hypothalamus, leptin is a very important hormone. Leptin binds to its receptors, triggering a cascade of chemical signals that alter appetite and aid in the production of satiety. Leptin, produced by fat cells, regulates biological behavior and metabolism by binding to central nervous system receptors. Leptin deficiency or resistance can lead to severe obesity in humans.

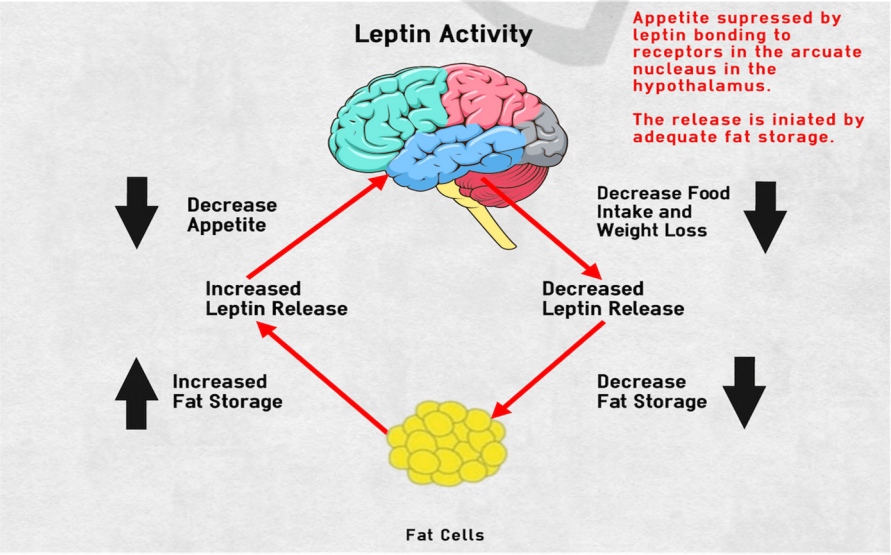

Figure 1: Leptin Activity (Chuck 2021).

This figure shows where leptin comes from and how it works in the most basic way. Leptin is released from adipose tissue, and the larger the number of adipose tissues, the greater the amount of leptin released, and vice versa. At the hypothalamic location in the brain, leptin interacts with leptin receptors to signal satiety. In other words, leptin acts in the hypothalamus to control appetite based on fat storage levels. According to the figure, as fat storage increases, fat cells produce more leptin, which suppresses hunger in the hypothalamus and causes people to eat less. When people lose weight, their leptin levels would drop, and their appetite would returns. This graph depicts leptin activity in the average individual. When a person has a congenital leptin gene deficiency, fat cells do not release leptin hormone, and leptin receptors in the hypothalamus do not receive leptin hormone regardless of fatness, and hence do not control appetite. Finally will lead to severe obesity.

2.1.2 MC4R

In addition to the congenital deficiency of the leptin gene, another gene that affects food intake leading to obesity is the melanocortin-4 receptor gene (MC4R), it is also considered to be the most common monogenic form of obesity in humans (Chung 2012) "MC4R is a single exon gene on chromosome 18q21.3. It encodes a G-protein coupled receptor expressed mainly in the brain." (Abdullah 2016) In the hypothalamus, the melanocortin-4 receptor gene (MC4R) is a key regulator of energy balance, food intake, and body weight. (Doulla 2021) As mentioned earlier, leptin acts mainly on neurons in the arcuate nucleus of the hypothalamus and in the fasting state, a decrease in leptin increases food intake by stimulating agouti-related peptide (AgRP) neurons. At the same time, leptin inhibits POMC neurons and reduces the amount of alpha-MSH (melanocyte-stimulating hormone), which normally inhibits food intake. Second-order neurons with melanocortin-4 receptors (MC4R) synthesize and integrate these signals.

The main clinical features of MC4R deficiency are hyperphagia, increased appetite, and impaired satiety. Adults with MC4R deficiency had significantly lower blood pressure and a decreased risk of hypertension than those of same age and weight. (Melanocortin 2021) The heart rate and sympathetic tone values are generally lower in patients with MC4R deficiency. Patients with MC4R deficiency have difficulty achieving weight loss because people tend to be less responsive to diet and exercise.

Complete deletion of MC4R also occurs and it is similar to the symptoms of MC4R deficiency. Abdullah, S and Reginold, W etc. reported a 4.5-year-old child with a complete deletion of one copy of MC4R. The young child presented obesity, tall stature, overall developmental delays, and sexual equality. (Abdullah 2016) The report also states that the child weighed 7 pounds 4 ounces at birth and had poor growth until 15 months of age when he began to gain weight rapidly. He had gained a lot of weight by the time he was 18 months old owing to his regular overeating.

2.2 Energy Expenditure

2.2.1 UCP1

Human energy consumption depends on many factors such as gender, age, and weight. A huge part of the factors related to energy expenditure that leads to obesity is due to the brown adipose tissue (BAT) (Pravednikova 2020) and the uncoupling protein (UCP) that are mainly found in the mitochondria of brown cell tissues. Therefore, the study of the UCP family can be of great help to the causes of obesity.

Uncoupling protein 1(CUP1) is a mitochondrial membrane protein involved in brown adipocyte adaptive thermogenesis. UCP1 is the only component that is capable of transporting protons across the inner membrane of mitochondria in brown adipocytes. In this mechanism, UCP1 acts as a proton carrier that is activated by free fatty acids, producing a shunt between respiratory chain complexes and ATP synthase. When UCP1 is active, the uncoupling process results in a futile cycle and the loss of oxidative energy as heat.

Theoretically, UCP1 deficiency should lead to a decrease in fat burning capacity and then lead to obesity. Kozak, L's articles8 have proposed experiments with mice because brown adipose tissue is the primary source of heat supply in mice, and there is little brown adipose tissue in adults that corresponds to that of mice. Interestingly, it has been shown from mouse experiments that UCP1 deficiency causes mice to be forced to use other thermogenic, metabolic systems, so UCP1 deficiency does not cause obesity in mice. In other words, UCP1 deficiency is not the leading cause of congenital obesity in children or people. (Kozak 2005) However, mice that lack UCP1 were more likely to develop fat accumulation with age than normal mice in the experiment. This experiment also proves that people with UCP1 deficiency are more likely to develop

obesity as they age than the general population. (Kontani 2005)

2.2.2 Beta 3-Adrenergic Receptors

β3 adrenergic receptors (β3-AR) are found on the cell surface of both white and brown adipocytes and are involved in lipolysis and thermogenesis. In humans, β3-ARs are widely expressed in brown adipose tissue, while white adipose tissue has few or no receptors. The relationship between β3-ARs and UCP1 is inextricably linked in terms of heat production. Uncoupling protein -1 is primarily responsible for the thermogenic activity of brown adipose tissue. Hypothermia stimulates Ucp1 gene expression via the sympathetic nervous system and -adrenergic receptors. (Razzoli 2018)

Variants or absence of β3-ARs can lead to obesity or less energy expenditure. (Clément 1970) Most of the β3-ARs mutations are mutations in the Trp64Arg of the β3-ARs, which can lead to an increased probability of weight gain, insulin resistance, or dyslipidemia, as well as a lower-body metabolic rate. Defects in 3-adrenergic receptor binding, signaling, or regulatory processes in obese people with such mutations may result in reduced lipolytic reactions in adipose tissue, aggravating obesity.

2.3 Fat Synthesis

The previous two parts examined the effect of genes on appetite and thermogenesis on obesity, starting from food intake and energy expenditure respectively. The main direction of this paragraph is about the relationship between fat storage and production and obesity. (Lazar 2004)

In adipogenesis, peroxisome proliferator-activated receptors γ are the primary regulators of adipogenesis. The most abundant expression of PPAR is found in adipose tissue, and two different PPARγ isoforms, PPARγ1 and PPARγ2, have been identified. Cells are also found in other organs, such as breast, colon, liver, and vascular cells. The expression of the PPARγ2 isoform appears to be entirely adipocyte specific.(Stienstra 2007) Adipogenesis is dependent on PPAR, and PPAR target genes regulate adipocyte differentiation, lipid storage, and glucose metabolism. In the liver, PPARγ is able to balance triglycerides and helps contribute to steatosis. At the same time, PPARγ in the liver protects other tissues from triglyceride accumulation and insulin resistance. In addition to this, PPARγ is also involved in managing inflammatory responses and has been shown to reverse macrophage infiltration and thus reduce inflammatory gene expression.

Therefore, PPARγ plays an essential role in our bodies. When there is a deficiency or variation of such an important gene, the body can suffer serious consequences. This issue was confirmed in mouse experiments, where mice's previous adipose-specific knockdown of the PPARγ gene did not show a dramatic phenotype in vivo. However, a specific mouse type, Adipoq-Cre mice, was used to drive adipose-specific recombination during the experiments. At 3 months of age, there is little visible brown and white adipose tissue, according to reports. As a result, mice appeared to have hugely enlarged pancreatic islets, massive fatty liver, and dramatically increased blood glucose and serum insulin levels with extreme insulin resistance. (Wang 2003) All of which are major complications of obesity and common pathophysiological bases for the development of metabolic disorders and other chronic diseases in obese populations.

3 TREATMENTS

3.1 Congenital Leptin Deficiency (Leptin Injection)

Congenital leptin deficiency is a specific condition that causes obesity and is relatively simple to treat. Daily subcutaneous injections of recombinant human leptin have been shown to be effective in treating congenital leptin deficiency, resulting in persistent beneficial effects on weight reduction, reduced hunger, normal pubertal development, and hyperinsulinemia, according to theoretical and clinical instances.

During the treatment process, some considerations need to be taken into account. Before the injection may be administered, the patient must first be clinically examined for an endocrine, sympathetic, and immunological function to confirm that they are normal. There are examples of clinical use of recombinant methionyl human leptin (r-metHu Leptin, Amylin Pharmaceuticals, San Diego, USA). In addition to this leptin, injections need to be administered at low physiological doses and need to mimic the normal circadian rhythm of leptin, usually starting at 6 pm. (Paz-Filho 2009) This article confirmed that the body composition, food intake and energy expenditure, lipid and glucose metabolism, sympathetic tone, and gonadal, adrenal, somatic, and thyroid functions are all affected by treatment.

Somatic and thyroid functions. The article also mentions other conditions affected by leptin include obesity, steatosis syndrome, diabetes, hypothalamic amenorrhea, and anorexia nervosa. (Paz-Filho 2010)

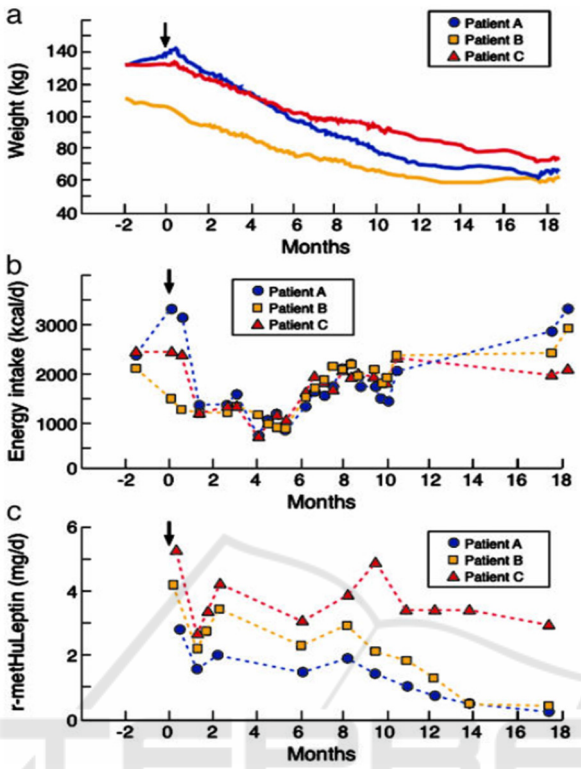

Figure 2: The effect of leptin treatment in adults (Licinio 2021)

These three graphs were produced by Julio Licinio, Sinan Caglayan et al. for three leptin-deficient adults treated with r-metHuLeptin injections for 18 months. In Figure A, it can be seen that all three patients had significant weight loss. During the treatment process, the three patients lost weight without any dietary changes or additional daily activities. Figure B shows the energy intake of the three patients. It shows a relationship between weight loss and energy intake. R-metHuLeptin injections suppressed their appetite and allowed them to lose weight by reducing their energy intake. All three individuals had significant weight loss after 18 months of treatment. Patient A, for instance, lost more than half of his initial body weight. These graphs reveal that leptin injections can effectively cure patients with congenital leptin deficiency.

3.2 MC4R Deficiency (Bariatric Surgery or Injections of Liraglutide)

MC4R gene mutations, also called MC4R deficiency, are divided into homozygous and heterozygous mutations. There are corresponding treatments for both mutations; Obesity is linked to heterozygous MC4R mutations in a dominantly inherited manner. MC4R deficiency affects around 2-5 percent of obese children, 1% of obese adults, and about 1/500 of the general population, making it the most prevalent single-gene cause of obesity. (Melanocortin 2021) The treatment for MC4R heterozygous mutations is bariatric surgery, called Roux-en-Y-bypass surgery. The size of the upper stomach will be reduced to a tiny pouch roughly the size of an egg with this operation. This will result in weight loss, however, in those who have homozygous mutations, this procedure may not be beneficial. The treatment for patients with homozygous mutations is injections of liraglutide, a GLP-1 receptor agonist that causes weight loss by reducing appetite. The example of obese people with the pathogenic MC4R mutation treatment resulted in an average weight loss of 6.8 kg. (Iepsen 2018) Overall fat, waist circumference, fasting, and postprandial glucose concentration were all decreased in a comparable way. As a result, liraglutide might be an effective therapy for obesity's

most frequent homogenous mutation.

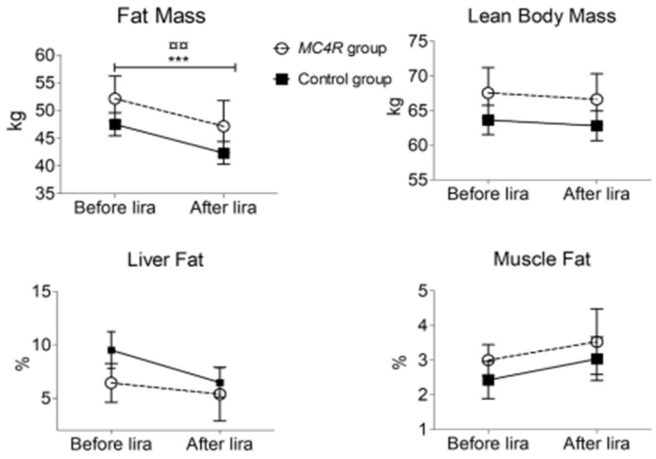

Figure 3: Results of liraglutide treatment for 14 people during 16 weeks (Iepsen 2018).

This graph is a comparison graph of 14 people treated with liraglutide for 16 weeks done by Eva W. Iepsen, Jinyi Zhang, et al. The graph shows the comparison of fat mass, lean body mass, liver mass, and muscle fat. There is a significant decrease in fat mass in both MC4R deficient and controlled groups. In addition, lean body mass and liver mass also decreased. This fully demonstrates that liraglutide treatment is helpful in MC4R deficient group. It is a very good treatment option.

3.3 UCP Deficiency (Rosiglitazone)

UCP deficiency is not a direct cause of obesity in people, but UCP deficiency can make that group of people more susceptible to obesity. Moreover, UCP is involved in the thermogenesis of brown fat which helps burn fat. If UCP is deficient, the body will be forced to use other thermogenic systems, which is one less way to help the body burn fat and is another form of obesity causing factor. Thus, the way to treat UCP deficiency is to take rosiglitazone (Rosi), which is a PPAR gamma agonist, usually in the form of a pill. It can be taken with or without meals at regular times. This drug was shown to be used in the treatment of UCP because, in primary cultures of brown adipocytes, rosiglitazone has an "exogenous" effect and induces p44/p42 and p38 mitogen-activated protein kinase (p38MAPK) activation. The latter is involved in the expression of the UCP-1 gene. Thus, the action of Rosi can lead to a high increase in transcriptional activity on the UCP-1 enhancer, leading to thermogenic effects. (Teruel 2002) Ultimately it will help patients to stimulate thermogenesis and fat oxidation in humans.

3.4 Beta 3-Adrenergic Receptors Mutation (Mirabegron)

People with mutations in the beta3-adrenergic receptor gene (Trp64Arg) typically develop non-insulin-dependent diabetes with a low metabolic rate, as well as increased body weight. Treatment is with Mirabegron, a beta3-AR agonist that effectively activates BAT. It will enhance glucose homeostasis and treat several of the underlying mechanisms of insulin resistance, such as insulin sensitivity and secretion, while also improving adipose tissue and inflammation. Mirabegron begins to work within a few hours but may take several weeks to reach full effect. (Finlin 2020)

3.5 PPARγ (Thiazolidinediones)

PPARγ is expressed predominantly in fat and very low in the liver and muscle. PPARγ deficiency leads to severe lipoatrophy, insulin resistance, and other associated metabolic disorders. In addition to its effects on obesity, PPARγ has a major impact on hair formation, breast growth, and increased bone mass. Thus, PPARγ is an important regulator of the development and function of these adipose-containing tissues. The treatment of PPARγ is with thiazolidinediones (TZD). TZD is a synthetic ligand for PPARγ. PPAR improves glucose and lipid absorption, boosts glucose oxidation, decreases free fatty acid concentrations, and reduces insulin resistance via activating numerous genes in tissues.

Among the studied genetic defects that cause obesity, congenital leptin deficiency is the least frequent one, and it occurs in childhood. MC4R is the most common genetic defect that causes obesity, and its treatment is more straightforward than other genes. One method is bariatric surgery, and the other is liraglutide injections, which act as an appetite suppressant. UCP deficiency does not lead to direct obesity. Still, the study of mice have shown that UCP deficiency can lead to a higher risk of future obesity than in the general population. Both β3-AR and PPARγ genes are critical, and deficiency is associated with obesity and metabolic problems. In particular the master gene PPARγ can cause problems in many-body functions. β3-AR is treated with Mirabegron. Mirabegron is an agonist of β3-AR itself, and PPARγ is somewhat similar to β3-AR, but is treated with Thiazolidinedione, which is a PPARγ agonist, is also used to stimulate PPARγ to treat obesity. Although TZD is beneficial for obesity and insulin resistance, some studies have shown that the use of TZD, the synthetic ligand of PPARγ, leads to bone-crunching, which allows for higher fracture rates. Rosiglitazone inhibits osteoblast differentiation and activates osteoclast differentiation, leading to bone loss due to reduced bone formation and increased bone resorption. (Wei 2011) Therefore, more researches are needed to find better solutions to the problem of PPARγ deficiency.

4 CONCLUSIONS

This paper mainly focuses on the causes and possible solutions of obesity caused by genes and metabolism in populations with different genetic defects. And also, this study has successfully summarized and concluded the effects of each gene congenital or mutation and the corresponding treatment options. However, during the research process, it was found that some genes, such as the UCP1 gene defect, do not respond significantly in human bodies but are inferred from experiments in mice, and further clinical studies are needed in the future. Also, most of the treatments found in this study were pharmacological, and the PPARγ treatment drug Thiazolidinediones had significant side effects, which needs to be further investigated in the future treatment of PPARγ gene defects.

REFERENCES

Abdullah, S., Reginold, W., Kiss, C., Harrison, K. J., & MacKenzie, J. J. (2016, September 21). Melanocortin-4 receptor deficiency phenotype with an interstitial 18q deletion: A case report of severe childhood obesity and tall stature. Case Reports in Pediatrics. Volume 2016, 6

Abdullah, S., Reginold, W., Kiss, C., Harrison, K. J., & MacKenzie, J. J. (2016, September 21). Melanocortin-4 receptor deficiency phenotype with an interstitial 18q deletion: A case report of severe childhood obesity and tall stature. Case Reports in Pediatrics. Volume 2016, 6

Chen, Y., Zhang, F., Heiman, M., & Dimarchi, R. (2005). Leptin: Structure, function and biology. Vitamins and hormones. volume71:345-372.

Chng, W. K. (2012, January). An overview of mongenic and syndromic obesities in humans. Pediatric blood & cancer. 58(1): 122–128.

Chuck, H. (2021, March 25). Leptin the appetite suppressor hormone. Walking Off Pounds. Retrieved October 27, 2021, from http://walkingoffpounds.com/leptin-the-appetite-suppressor-hormone/.

Clément, K., Al., E., Author AffiliationsFrom the Centre National de la Recherche Scientifique, Others, A. J. and, Others, C. A. B. and, Others, M. E. and, Others, J. K. and, Others, N. B. and, & J. Lopez Bernal and Others. (1970, September 2). Genetic variation in the β3-adrenergic receptor and an increased capacity to gain weight in patients with morbid obesity: Nejm. New England Journal of Medicine. 333,352-354

Doulla, M., McIntyre, A. D., Hegele, R. A., & Gallego, P. H. (2014, December). A novel MC4R mutation associated with childhood-onset obesity: A case report. Paediatrics & child health. 19(10): 515–518.

Finlin, B. S., Memetimin, H., Zhu, B., Confides, A. L., Vekaria, H. J., Khouli, R. H. E., Johnson, Z. R., Westgate, P. M., Chen, J., Morris, A. J., Sullivan, P. G., Dupont-Versteegden, E. E., & Kern, P. A. (2020, May 1). The β3-adrenergic receptor agonist mirabegron improves glucose homeostasis in obese humans. The Journal of Clinical Investigation. 130(5):2319-2331

Gao. M., Liu. D. (2014) Gene Therapy for Obesity: Progress and Prospects, https://www.discoverymedicine.com/Mingming-Gao/2014/06/gene-therapy-for-obesity-progress-and-prospects/

Kontani, Y., Wang, Y., Kimura, K., Inokuma, K.-I., Saito, M., Suzuki-Miura, T., Wang, Z., Sato, Y., Mori, N., & Yamashita, H. (2005, May 9). Ucp1 deficiency increases susceptibility to diet-induced obesity with age. Wiley Online Library. Aging Cell 4, 147–155

Kozak, L. P., & Anunciado-Koza, R. (2008, December). Ucp1: Its involvement and utility in obesity. International journal of obesity (2005). 32(Suppl 7): S32–S38.

Lazar, M. A. (2004, November 18). PPARγ, 10 years later. Biochimie. 87: 9–13

Licinio, J., Caglayan, S., Ozata, M., Yildiz, B. O., de Miranda, P. B., O'Kirwan, F., Whitby, R., Liang, L., Cohen, P., Bhasin, S., Krauss, R. M., Veldhuis, J. D.,

Wagner, A. J., DePaoli, A. M., McCann, S. M., & Wong, M.-L. (2004, March 30). Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. Proceedings of the National Academy of Sciences of the United States of America. Retrieved October 28, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC384781/. 101(13): 4531–4536 doi: 10.1073/pnas.0308767101

Melanocortin 4 Receptor. (2021, August 23). Accessed September 6, 2021. https://www.mc4r.org.uk/

Paz-Filho, G., Delibasi, T., Erol, H. K., Wong, M.-L., & Licinio, J. (2009, November 4). Congenital leptin deficiency and thyroid function. Thyroid research. 2: 11. doi: 10.1186/1756-6614-2-11

Paz-Filho, G., Mastronardi, C., Delibasi, T., Wong, M.-L., & Licinio, J. (2010, November). Congenital leptin deficiency: Diagnosis and effects of leptin replacement therapy. Arquivos brasileiros de endocrinologia e metabologia. 54(8): 690–697.

Pravednikova, A. E., Shevchenko, S. Y., Kerchev, V. V., Skhirtladze, M. R., Larina, S. N., Kachaev, Z. M., Egorov, A. D., & Shidlovskii, Y. V. (2020, May 25). Association of uncoupling Protein (ucp) gene POLYMORPHISMS With CARDIOMETABOLIC DISEASES. Molecular medicine (Cambridge, Mass.). 26: 51. doi: 10.1186/s10020-020-00180-4

Razzoli, M., Emmett, M. J., Lazar, M. A., & Bartolomucci, A. (2018, May 1). β-Adrenergic receptors Control brown adipose UCP-1 tone and cold response without affecting ITS circadian rhythmicity. Federation of American Societies for Experimental Biology. Volume 32, 5640 - 5646

Stienstra, R., Duval, C., Müller, M., & Kersten, S. (2007). Ppars, obesity, and inflammation. PPAR research. Volume 2007: 95974. doi: 10.1155/2007/95974

Teruel, T., Hernandez, R., Benito, M., & Lorenzo, M. (n.d.). Rosiglitazone and retinoic ACID induce uncoupling PROTEIN-1 (UCP-1) in a p38 mitogen-activated Protein kinase-dependent manner in fetal primary brown adipocytes. The Journal of biological chemistry. 278(1):263-9. doi: 10.1074/jbc.M207200200.

W Iepsen, E., Zhang, J., S Thomsen, H., L Hansen, E., Hollensted, M., Madsbad, S., Hansen, T., J Holst, J., Holm, J.-C., & S Torekov, S. (n.d.). Patients with obesity caused By Melanocortin-4 receptor mutations can be treated with A Glucagon-like Peptide-1 receptor agonist. Cell metabolism. 28(1):23-32. e3. doi: 10.1016/j.cmet.2018.05.008.

Wang, F., Mullican, S. E., DiSpirito, J. R., Peed, L. C., & Lazar, M. A. (2013, November 12). Lipoatrophy and severe metabolic disturbance in mice WITH fat-specific deletion of pparγ. Proceedings of the National Academy of Sciences of the United States of America. 110(46): 18656–18661. doi: 10.1155/2007/95974

Wei, W., & Wan, Y. (2011, October 29). Thiazolidinediones on pparγ: The roles in bone remodeling. PPAR Research. vol. 2011,9. doi.org/10.1155/2011/867180

Xu, H., Barnes, G. T., Yang, Q., Tan, G., Yang, D., Chou, C. J., Sole, J., Nichols, A., Ross, J. S., Tartaglia, L. A., & Chen, H. (2003, December). Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. The Journal of clinical investigation. 112(12): 1821–1830. doi: 10.1172/JCI19451