Asian Journal of Medicine and Health
3(3): 1-12, 2017; Article no.AJMAH.32146

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Obesity: Multiple Biological Factors

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Authors' contributions

This work was carried out in collaboration between both authors. Author ARC designed the study. Author SA wrote the first draft of the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2017/32146
Editor(s):
(1) Maria Manuel Azevedo, Department of Microbiology, Faculty of Medicine, University of Porto, Porto, Portugal.
Reviewers:
(1) Fethi Ben Slama, National Institute of Public Health, Tunisia.
(2) Sunday Akau Hena, Usmanu Danfodiyo University, Sokoto, Nigeria.
Complete Peer review History: http://www.sciencedomain.org/review-history/18348

Review Article

Received 10th February 2017
Accepted 14th March 2017
Published 25th March 2017

ABSTRACT

Obesity is one of the major challenge of modern society which will lead to other health problems. Recently, researches have been conducted to understand the correlation between obesity and type of gut microflora with the objective to control severe health diseases by changing gut flora or diet. Researches also have been conducted to understand the relationship of serum leptin and obesity. Leptin is a hormone produced by white adipose tissue that acts as a satiety factor sending signals of nutritional status to the hypothalamus. Both gut microflora, as well as serum leptin, have shown significant associations with obesity individually and in relation to each other. However due to the great heterogeneous and complex nature of obesity, the question regarding their interaction with each other remains unclear. The objective of review are, firstly to identify the role of gut microflora & serum leptin; secondly, to analyse the interaction of gut microflora and serum leptin in the obese phenotype and lastly, to discuss the therapeutic benefits of gut microflora modulation for serum leptin.

Keywords: Gut microflora; leptin; obesity; probiotics; prebiotics.

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ABBREVIATIONS

ARC : Hypothalamic arcuate nucleus
VAN : Vagal afferent neurons
JAK/STAT : Janus kinase/ signal transducers and activators of transcription
SOCS : Suppressors of cytokine signalling
CONV-R : Conventionally raised
GF : Germ free
HFD : High fat diet
LPS : Lipopolysaccharide

1. INTRODUCTION

Obesity is a growing worldwide epidemic affecting nearly 1.9 billion people as of 2014 [1] and the numbers continue to rise. It is caused by an imbalance in energy intake and expenditure resulting in increased body weight, metabolic dysfunction and chronic low grade inflammation [2]. It is a risk factor for the development of chronic non-communicable diseases with high morbidity such as diabetes and cardiovascular disorders [3]. In addition to negatively altering health conditions and lifestyle it is becoming an ever growing economic burden [4,5]. Many factors affect the development and the progression of obesity including genetics, age, sex and environment [6,7].

There has been growing interest in the association of gut microflora as an environmental factor in obesity [8]. There are trillions of microorganisms and 1000 bacterial species living the human gastrointestinal tract [9]. For many years gut microflora were thought to simply live in the gastrointestinal tract without directly affecting the host, however recent research is suggesting otherwise. This huge load of microorganisms has its own genes and metabolic reactions which affects human health as the microorganisms are in direct contact with a mucosal absorptive surface with a rich blood supply and significant immunological function [10].

There has also been keen interest in the relationship of serum leptin and obesity. Leptin is a hormone produced by white adipose tissue that acts as a satiety factor sending signals of nutritional status to the hypothalamus. It affects food intake, metabolism, controls appetite and energy expenditure [11,12]. A rise in body fat mass increases serum leptin levels hence triggering satiety and inhibiting food intake. However leptin resistance develops in obese individuals causing a disruption in its function [13]. Therefore identifying the factors that lead to leptin resistance can help to combat weight gain and gut microflora is a promising factor in this aspect.

Both gut microflora as well as serum leptin have shown significant associations with obesity individually and in relation to each other. However due to the great heterogeneous and complex nature of obesity the question regarding their interaction with each other remains unclear. This review aims to answer this question by firstly identifying the role of gut microflora and serum leptin; secondly analysing the interaction of gut microflora and serum leptin in the obese phenotype and thirdly discussing the therapeutic benefits of gut microflora modulation for serum leptin.

2. LEPTIN AND LEPTIN RESISTANCE

Adipose tissue act as an energy storage site as well as an endocrine tissue that releases various adipokines affecting glucose and lipid metabolism [14,15]. Leptin is one such hormone produced by adipose tissue in proportion to fat mass [16]. It regulates appetite, satiety, food intake and energy expenditure [11,12]. An increase in fat mass results in an increase in serum leptin levels which in turn inhibits food intake as there is sufficient stored energy in the body. As a result, mutation and defects in leptin production or the function of leptin receptor results in increase appetite, hyperphagia and severe early onset obesity [17–19].

Leptin receptor is a single membrane spanning protein comprising of several isoforms with the long isoform LebRb being the primary signalling isoform [20–22]. Leptin receptors are found mainly on the hypothalamic arcuate nucleus (ARC) [23] but they can also be found in vagal afferent neurons (VAN) [24]. Activation of leptin receptor is achieved through the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway [25] which is regulated by suppressors of cytokine signalling (SOCS) family of proteins in particular SOCS-3 [26].

Despite the high levels of serum leptin in obese individuals it does not cause weight loss and administration of exogenous leptin to obese individuals does not promote weight loss either, hence suggesting the development of leptin resistance in obesity [13]. Over expression of

SOCS-3 is suggested to cause leptin resistance where increased leptin increases SOCS-3 expression and decreases leptin receptor signalling [27].

Experiments on rat models show that hypothalamic leptin resistance develops after hyperphagia and obesity [28] whereas leptin resistance in VAN coincides with hyperphagia [29] suggesting that resistance in hypothalamic neurons does not initiate hyperphagia and obesity. In fact deletion of leptin signalling by knocking out leptin receptor expression in VAN lead to hyperphagia and obesity by preventing post prandial gut brain signalling [30]. This suggest that VAN are involved in the initiation of leptin resistance.

3. GUT MICROFLORA

Gut microflora have been shown to increase energy absorption in the intestine by breaking down indigestible products and making them available for absorption and utilisation [31–33]. Studies comparing conventionally raised (CONV-R) mice and germ free (GF) mice found that food intake is lower in CONV-R mice but they weighed more than the GF mice with the GF mice free from high fat diet (HFD) associated metabolic dysfunction [32,34,35]. Inversely, implanting gut microbiota from CONV-R obese mice into GF mice caused an increase in body fat and insulin resistance in the GF mice [36,37]. The gut microflora increased adiposity in the animals despite reduced food intake supporting the suggestion that gut microbes increase energy absorption from food.

Changes in the composition of gut microflora have been reported in obese individuals of both animal and human models (as summarised in Table 1). However, there have been conflicting reports on the nature of these changes. Some human studies have found an increase in the *Firmicutes* to *Bacteroides* ratio with relative decrease in *Bacteroides* and an increase in *Firmicutes* in the obese individuals compared to their lean counterparts [38]. These findings were mirrored in several studies involving obese mice, high fat diet induced obese mice [39–41] as well as Beagle dogs [42]. However not all studies corroborated these exact observations [43,44].

4. LEPTIN AND GUT MICROFLORA

4.1 Gut Microflora and Leptin Receptors

LebRb-defficient mice were used to determine the presence of a link between leptin signalling and gut microflora. Pair fed LepRb-defficient mice had an increased ratio of *Firmicutes* to *Bacteroidetes* in comparison to wild-type pairs. A change similar to that found in obese mice. This shows that leptin signalling affects gut microflora independently of other factors such as diet and body weight [50].

Inversely there is evidence indicating that gut microbiota can reduce leptin sensitivity. A study showed an upregulation of SOCS-3, an inhibitor of cytokine signalling [26] associated with leptin resistance [27] in CONV-R mice but not in GF mice. Exogenous administration of leptin caused a significant drop in body weight of GF mice but not in CONV-R mice. This shows that the presence of gut microflora directly affects leptin levels by decreasing leptin inhibition possibly leading to or accelerating leptin resistance [51].

4.2 Bacterial Cell Wall Component

A hypothesis suggests that the breakdown of the bacteria is what triggers obesity by causing metabolic endotoxaemia. Metabolic endotoxaemia is an increase in bacterial cell wall component lipopolysaccharide (LPS) in the blood stream [52]. This condition is characteristic of many metabolic diseases and is thought to

Table 1. Studies linking obesity and gut microflora alterations in human and mouse models

Studies	Model	Phenotype	Microflora alteration
[38]	*Homo sapien* Human	Obesity	Increased *Firmicutes* : *Bacteroides* ratio
[8]	*Homo sapien* Human	Obesity	Decreased diversity Decreased *Bacteroides*
[32,34,45–48]	*Mus musculus* mouse	Increased adiposity, weight gain and insulin resistance	Whole microbiome
[33,36,37,49]	*Mus musculus* mouse	Increased adiposity and obesity	Increased *Firmicutes* : *Bacteroides* ratio

initiate obesity [52–54] by many mechanisms including adipose tissue inflammation and stimulating adipose progenitor cells [55].

Chronic exposure to LPS has been found to inhibit secretion of leptin [39]. On the other hand, a study on mice found that chronic LPS stimulation decreases vagal afferent signalling resulting in the subsequent decrease of leptin-induced STAT3 phosphorylation, however these changes were not observed in hypothalamic leptin signalling [56]. Increased vagal stimulation can cause hyperphagia increasing energy intake and further altering the gut microflora and intestinal barrier function [57] as HFD significantly increases intestinal permeability [45,58].

These findings when combined, suggest that a HFD decreases membrane barrier function resulting in increased LPS in the blood causing impaired leptin receptor signalling via decreased STAT 3 phosphorylation as well as decreased vagal afferent signalling causing hyperphagia. Hence a possible mechanism between HFD induced gut microflora changes and impaired leptin signalling/function is obtained.

This effect was not found in gram positive bacterial cell wall components. Therefore it has been suggested that addition of gram positive bacteria like *Lactobacillus* and *Bifidobacterium* may ameliorate the effects of LPS by being the competitive alternative [39].

4.3 Autoimmunity

Gut microbes release many molecules into the intestinal environment due to regular metabolism or breakdown. The intestinal tract is rich with Payer's patches and peripheral lymphoid tissue, to monitor and protect the intestinal environment as necessary by producing antibodies, especially IgA as it is a mucous membrane [59].

IgA and IgG autoantibodies against appetite-regulating peptides including leptin were found in the sera of health humans [60,61]. This could be part of the physiological control of appetite-regulating peptide and the presence of IgA suggest possible involvement of luminal antigens including gut microflora. Though the presence of these autoantibodies is not dependent on gut microflora, as they are also found in GF mice, the levels of autoantibodies can be altered by the composition of gut microflora.

Using the concept of molecular mimicry, commensal and pathogenic intestinal flora were examined for peptide fragments similar to any part of different appetite-regulating peptides. *Lactococcus lactis*, *Escherichia coli*, *Lactobacilli bacteriophage*, *Yarrowia lipolytica*, *Candida*, and *Aspergillus* species and *Streptococcus* had peptide fragments identical to leptin [61]. These results suggest that the presence of or infection with these bacteria could result in production of autoantibodies against leptin.

This information provides useful and pragmatic insight to possible treatment options of obesity and leptin resistance through gut microflora. Increasing production of autoantibodies via immunisation or supplementation of these bacteria can help decrease hyperleptinemia and in turn manage leptin resistance in obesity. However, more work is required in this aspect.

4.4 Other Peptide Hormones and Adipokines

Due to the heterogeneous nature of obesity it is important to note that a few hormones and adipokines that contribute to obesity, and indirectly to the problem of leptin resistance, are also affected by gut microflora.

Leptin is one of many hormones and cytokines secreted by adipose tissue, also known as adipokines. Adipokines that are commonly associated with obesity and metabolic dysfunction include adiponectin and resistin. An increase in circulating bacterial cell wall

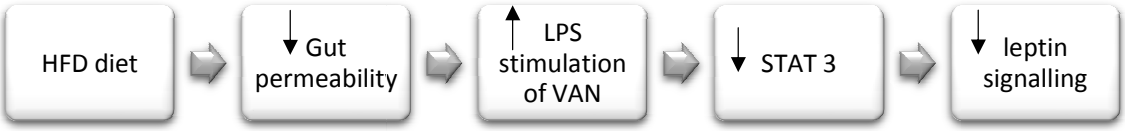

Fig. 1. Decreased leptin signalling by metabolic endotoxaemia

components, like LPS as seen in metabolic endotoxamia has been shown to mediate an increase in adiponectin, resistin and leptin [39]. This metabolic endotoxaemia coupled with the inflammatory effects of adipokines results in increased systemic inflammation which contributes to obesity and in turn leptin resistance [62].

There is well documented correlation between the incidence of type 2 diabetes and obesity [63]. Insulin is peptide hormone which is essential in healthy glucose metabolism [64]. Type 2 diabetes is characterised by insulin resistance which seems to be affected by gut microflora composition in a similar way to obesity [2,35,48,65]. Increased circulating levels of leptin have been associated with insulin resistance [66]. Understanding the role of gut microflora in metabolic diseases that coincide with obesity can help in managing obesity and leptin resistance further down the line.

Ghrelin, a peptide hormone that stimulates hunger and increases food intake [67] is also affected by gut microflora compositions [68]. Since hunger plays a part in hyperphagia, modulation of ghrelin levels through modulation of gut microflora composition may be a potential avenue to decreasing hyperphagia.

5. THERAPEUTIC APPLICATION OF GUT MICROFLORA MODULATION

It is becoming increasing clear that gut microflora is an important element in leptin control and obesity. Therefore modulating it would prove a beneficial therapeutic option. Gut microflora can be altered either by introducing beneficial bacteria (probiotics), consuming food that enhance the growth of certain bacteria (prebiotic) or consuming other compounds that alter the environment and either reverse or prevent the dysbiosis found in obese people.

5.1 Probiotics

Probiotics are live microorganisms that, when ingested in sufficient amounts provide health benefits to the host [69]. They come in many strains and confer benefits on various body systems including the gastrointestinal system.

Lactobacillus species has shown promising benefits with respect to obesity. Administration of *Lactobacillus plantarum* LG42, to HFD fed mice resulted in decreased adiposity, significant decrease in weight gain and a significant decrease in leptin levels compared to control [70]. *L. curvatus* HY7601 and *L. plantarum* KY1032 supplementation to diet induced obese mice lead to reduced body weight gain and gut microbiota modulation compared to non-supplemented group [71]. However studies using *Lactobacillus acidophilus* NCDC 13 [72] and *Lactobacillus plantarum* WCFS1 [58] didn't show significant change suggesting that the benefits are strain specific.

Bifidobacterium species is a commensal species that increases mucosal barrier function and decreases metabolic endotoxaemia [73,74]. it is decreased in HFD [75,76]. Oral administration of *Bifidobacterium pseudocatenulatum* CECT 7765 to HFD fed mice caused decreased caloric intake, decreased weight gain, decreased adipocyte size, reduced fat micelles in enterocytes and a decrease in leptin levels [77]. Supplementation with *L. curvatus* HY7601 and *L. plantarum* KY1032 showed an increase in the relative abundance of *Bifidobacterium pseudolongum* although it was not externally administered [71] suggesting this increase could have been a factor in the benefits seen.

The oral administration of *Bacteroides uniformis* CECT 7771 reduced body weight gain, liver steatosis and liver cholesterol and triglyceride concentrations and increased small adipocyte numbers in HFD fed mice. The strain also reduced serum cholesterol, triglyceride, glucose, insulin and leptin levels. *B. uniformis* CECT 7771 increased *Bifidobacterium* spp. and *Bacteroides* spp [75].

Akkermansia muciniphila is a mucin degrading bacteria found in the mucus layer of the gut [78]. In healthy individuals its abundance inversely correlates with body weight [40,79,80]. Administration of alive *A. muciniphila* to mice reversed high-fat diet-induced metabolic disorders, including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance [58].

5.2 Prebiotics

Prebiotics are non-digestible polysaccharides and oligosaccharides which promote the growth of beneficial intestinal microflora [81].

Table 2. Summary of gut microflora modulation methods

Modulation methods	Definition	Action	Example
Probiotics	Live microorganisms [69]	Decrease or reverse obesity induced gut microflora dysbiosis	*Lactobacillus* species [70,71] *Bifidobacterium* species [76,77] *Bacteroides* species [75] *Akkermansia muciniphila* [58]
Prebiotics	Non-digestible polysaccharides and oligosaccharides [81]	Decrease adiposity	Oligofructose [40]
Natural Products	Plants or plant derived compounds	Lowered serum leptin levels	Capsaicin (major capsaicinoid of red chilli peppers) [41] *Plantago maxima* leaf extract [83]

Oligofructose is a probiotic that has shown great benefit. Supplementation with oligofructose in obese mice decreased *Firmicutes* and increased *Bacteroidetes* phyla. It also improved glucose tolerance, reduced fat-mass development, oxidative stress, and low-grade inflammation as well as improved leptin sensitivity [40]. Oligofructose supplementation in HFD fed mice restored *Bifidobacterium* levels which in turn reduced metabolic endotoxemia and related pro-inflammatory factors [76].

5.3 Natural Products

The role of natural products and compounds in modulating obesity and serum leptin through gut microflora is a promising avenue. Two such products namely capsaicin and *Plantago maxima* leaves are good examples.

Capsaicin is the major capsaicinoid found in red chilli. Topical application of capsaicin was found to decrease visceral adiposity by reducing fat mass in adipose tissue as well as significantly decreasing lipid droplets in adipose tissue overall decreasing the occurrence of large adipocytes [82]. In a more recent study HFD fed mice were given capsaicin as a supplement. Capsaicin reduced the gut microflora alteration related to obesity (lower increase in the *Firmicutes* compared to control HFD). It enhanced mucus secretion, significantly inhibited increased body weight with HFD and reduced leptin secretion with HFD [41].

Plantago maxima supplemented to mice on a HFD showed a decrease in adipocyte area, reversed leptin elevation, prevented diet induced change of colonic gram-positive, a decrease in gram negative flora bacteria compared to control HFD mice. Therefore it reduced HFD caused dysbiosis, resulting in better leptin sensitivity and adipose tissue health [83].

6. CONCLUSION

Gut microflora directly and indirectly affects leptin levels in obesity by decreasing leptin sensitivity, inducing metabolic endotoxaemia and affecting the production of leptin specific antibodies by molecular mimicry. These aspects can be positively manipulated by modulating the gut microflora to include strains and species that support an intestinal environment with healthy gut barrier and metabolic function. Modulation can be done through probiotics, prebiotics as well as natural products. Many studies have demonstrated their benefits however there is a lack of sufficient human studies to solidify this evidence. Further studies into this aspect can hopefully involve inclusion of these modulation methods in mainstream obesity treatments in the near future rather than their current use just as supplements that are not available to all. Hence, giving hope of a more well-rounded treatment criteria that decreases the metabolic dysfunction in obesity and in turn decreases the risk of obesity induced chronic diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. WHO, Obesity and overweight. World Health Organization. [cited 2015 Aug 23] Available:http://www.who.int/mediacentre/factsheets/fs311/en/
2. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112(12):1821–30. [cited 2014 Dec 12] Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=296998&tool=pmcentrez&rendertype=abstract
3. WHO, Noncommunicable diseases. World Health Organization. [cited 2015 Sep 29] Available:http://www.who.int/mediacentre/factsheets/fs355/en/
4. Hammond RA, Levine R. The economic impact of obesity in the United States. Diabetes Metab Syndr Obes. 2010;3:285-95. [cited 2015 Jun 16]. Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3047996&tool=pmcentrez&rendertype=abstract
5. National Obesity Observatory. The economic burden of obesity. 2010;1–13.
6. Ramachandrappa S, Farooqi IS. Genetic approaches to understanding human obesity. J Clin Invest. 2011;121(6):2080–6.
7. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011;364(25):2392–404. [cited 2015 Feb 5] Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3151731&tool=pmcentrez&rendertype=abstract
8. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Ley RE, Sogin ML, et al. A core gut microbiom in obese and lean twins. Nature. 2009;457(32089):480–4.
9. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol. 2008;6(11):e280. [cited 2014 Jul 18] Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2586385&tool=pmcentrez&rendertype=abstract
10. Wells JM, Rossi O, Meijerink M, van Baarlen P. Epithelial crosstalk at the microbiota-mucosal interface. Proc Natl Acad Sci USA. 2011;108(Suppl):4607–14.
11. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998;395(6704):763–70.
12. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, et al. Role of leptin in the neuroendocrine response to fasting. Nature. Nature Publishing Group. 1996;382(6588):250–2. [cited 2015 Mar 16] Available:http://www.nature.com/nature/journal/v382/n6588/pdf/382250a0.pdf
13. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, et al. Recombinant leptin for weight loss in obese and lean adults. JAMA. American Medical Association. 1999;282(16):1568. [cited 2015 Aug 8] Available:http://jama.jamanetwork.com/article.aspx?articleid=192037
14. Flier JS. Obesity Wars. Cell. 2004;116(2): 337–50. [cited 2015 Sep 6] Available:http://www.sciencedirect.com/science/article/pii/S009286740301081X
15. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. Endocrinology. Endocrine Society. 2003;144(6):2195–200. [cited 2015 Sep 6] Available:http://press.endocrine.org/doi/10.1210/en.2003-0285?url_ver=Z39.88-2003&rfr_id=ori%253Arid%253Acrossref.org&rfr_dat=cr_pub%253Dpubmed&
16. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334(5):292–5. [cited 2015 Feb 5] Available:http://www.ncbi.nlm.nih.gov/pubmed/8532024
17. Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med. 2007;356(3):237–47.
18. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997;387(6636):903–8.

19. Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature. 1998;392(6674):398–401.
[cited 2015 Jun 17]
Available:http://dx.doi.org/10.1038/32911
20. Lee GH, Proenca R, Montez JM, Carroll KM, Darvishzadeh JG, Lee JI, et al. Abnormal splicing of the leptin receptor in diabetic mice. Nature. 1996;379(6566): 632–5.
[cited 2015 Jun 18]
Available:http://dx.doi.org/10.1038/379632a0
21. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell Elsevier. 1995;83(7):1263–71.
[cited 2015 Aug 6]
Available:http://www.cell.com/article/0092867495901515/fulltext
22. Bjorbaek C, Uotani S, da Silva B, Flier JS. Divergent signaling capacities of the long and short isoforms of the leptin receptor. J Biol Chem. 1997;272(51):32686–95.
[cited 2015 Sep 6]
Available:http://www.jbc.org/content/272/51/32686.long
23. Mercer JG, Hoggard N, Williams LM, Lawrence CB, Hannah LT, Trayhurn P. Localization of leptin receptor mRNA and the long form splice variant (Ob-Rb) in mouse hypothalamus and adjacent brain regions by in situ hybridization. FEBS Lett. Elsevier. 1996;387(2–3):113–6.
[cited 2015 Sep 6]
Available:http://www.febsletters.org/article/0014579396004735/fulltext
24. Burdyga G, Spiller D, Morris R, Lal S, Thompson D., Saeed S, et al. Expression of the leptin receptor in rat and human nodose ganglion neurones. Neuroscience. 2002;109(2):339–47.
[cited 2015 Sep 6]
Available:http://www.sciencedirect.com/science/article/pii/S0306452201004742
25. Ghilardi N, Skoda RC. The leptin receptor activates janus kinase 2 and signals for proliferation in a factor-dependent cell line. Mol Endocrinol Endocrine Society; 2013.
[cited 2015 Sep 6]
Available:http://press.endocrine.org/doi/10.1210/mend.11.4.9907?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%253dpubmed
26. Starr R, Willson TA, Viney EM, Murray LJL, Rayner JR, Jenkins BJ, et al. A family of cytokine-inducible inhibitors of signalling. Nature. 1997;387(6636):917–21.
27. Münzberg H, Flier JS, Bjørbaek C. Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. Endocrinology. 2004;145(11):4880–9.
[cited 2015 Sep 6]
Available:http://www.ncbi.nlm.nih.gov/pubmed/15271881
28. Myers MG, Leibel RL, Seeley RJ, Schwartz MW. Obesity and leptin resistance: Distinguishing cause from effect. Trends Endocrinol Metab. 2010;21(11):643–51.
[cited 2015 Mar 6]
Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2967652&tool=pmcentrez&rendertype=abstract
29. de Lartigue G, Barbier de la Serre C, Espero E, Lee J, Raybould HE. Diet-induced obesity leads to the development of leptin resistance in vagal afferent neurons. Am J Physiol Endocrinol Metab. 2011;301(1):E187-95.
[cited 2015 Sep 6]
Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3129833&tool=pmcentrez&rendertype=abstract
30. de Lartigue G, Ronveaux CC, Raybould HE. Deletion of leptin signaling in vagal afferent neurons results in hyperphagia and obesity. Mol Metab Elsevier GmbH. 2014;3(6):595–607.
Available:http://dx.doi.org/10.1016/j.molmet.2014.06.003
31. Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr. 2011;94(1):58–65.
[cited 2015 Apr 6]
Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3127503&tool=pmcentrez&rendertype=abstract
32. Bäckhed F, Ding H, Wang T, Hooper L V, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA. 2004;101(44):15718–23.
[cited 2014 Jul 9]
Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=524219&tool=pmcentrez&rendertype=abstract

33. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA. 2005;102(31):11070–5.
34. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci. 2007; 104(3):979–84.
[cited 2015 Mar 15]
Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1764762&tool=pmcentrez&rendertype=abstract
35. Rabot S, Membrez M, Bruneau A, Gérard P, Harach T, Moser M, et al. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. FASEB J. 2010;24(12):4948–59.
36. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 2008;3(4):213–23.
[cited 2014 Jul 19]
Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3687783&tool=pmcentrez&rendertype=abstract
37. Turnbaugh PJ, Ley RE, Mahowald M a, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027–31.
38. Ley R, Turnbaugh P, Klein S, Gordon J. Microbial ecology: Human gut microbes associated with obesity. Nature. 2006; 444(7122):1022–3.
Available:http://europepmc.org/abstract/MED/17183309
39. Taira R, Yamaguchi S, Shimizu K, Nakamura K, Ayabe T, Taira T. Bacterial cell wall components regulate adipokine secretion from visceral adipocytes. J Clin Biochem Nutr. 2015;56(2):149–54.
[cited 2015 Aug 12]
Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4345181&tool=pmcentrez&rendertype=abstract
40. Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GM, Neyrinck AM, et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. Diabetes. 2011;60(11): 2775–86.
41. Baboota RK, Murtaza N, Jagtap S, Singh DP, Karmase A, Kaur J, et al. Capsaicin-induced transcriptional changes in hypothalamus and alterations in gut microbial count in high fat diet fed mice. J Nutr Biochem. Elsevier Inc. 2014;25(9): 893–902.
Available:http://dx.doi.org/10.1016/j.jnutbio.2014.04.004
42. Park H-J, Lee S-E, Kim H-B, Isaacson RE, Seo K-W, Song K-H. Association of obesity with serum leptin, adiponectin, and serotonin and gut microflora in beagle dogs. J Vet Intern Med. 2015;29(1):43–50.
Available:http://doi.wiley.com/10.1111/jvim.12455
43. Duncan SH, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, et al. Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes (Lond). 2008;32(11):1720–4.
[cited 2015 Sep 15]
Available:http://www.ncbi.nlm.nih.gov/pubmed/18779823
44. Schwiertz A, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity. 2010;18(1):190–5.
[cited 2015 Apr 1]
Available:http://www.ncbi.nlm.nih.gov/pubmed/19498350
45. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, et al. Changes in gut microbiota control metabolic endotoxemia- induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008;57(6):1470–81.
[cited 2015 Mar 22]
Available:http://diabetes.diabetesjournals.org/content/57/6/1470.full
46. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010;328(5975):228–31.
[cited 2015 Jun 18]
Available:http://www.ncbi.nlm.nih.gov/pubmed/20203013
47. Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, et al. Inflammasome- mediated dysbiosis

regulates progression of NAFLD and obesity. Nature. 2012;482(7384):179–85. [cited 2014 Jul 13] Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3276682&tool=pmcentrez&rendertype=abstract

48. Caricilli AM, Picardi PK, de Abreu LL, Ueno M, Prada PO, Ropelle ER, et al. Gut microbiota is a key modulator of insulin resistance in TLR 2 knockout mice. PLoS Biol. 2011;9(12):e1001212. [cited 2015 Aug 17] Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3232200&tool=pmcentrez&rendertype=abstract
49. Murphy EF, Cotter PD, Healy S, Marques TM, O'Sullivan O, Fouhy F, et al. Composition and energy harvesting capacity of the gut microbiota: Relationship to diet, obesity and time in mouse models. Gut. 2010;59(12):1635–42. [cited 2015 Sep 28] Available:http://www.ncbi.nlm.nih.gov/pubmed/20926643
50. Rajala MW, Patterson CM, Opp JS, Foltin SK, Young VB, Myers MG. Leptin acts independently of food intake to modulate gut microbial composition in male mice. Endocrinology. 2014;155(3):748–57.
51. Schéle E, Grahnemo L, Anesten F, Halleń A, Bačkhed F, Jansson JO. The gut microbiota reduces leptin sensitivity and the expression of the obesity-suppressing neuropeptides proglucagon (Gcg) and brain-derived neurotrophic factor (Bdnf) in the central nervous system. Endocrinology. 2013;154(10):3643–51.
52. Neves AL, Coelho J, Couto L, Leite-Moreira A, Roncon-Albuquerque R. Metabolic endotoxemia: a molecular link between obesity and cardiovascular risk. J Mol Endocrinol. 2013;51(2):R51-64. [cited 2015 Sep 12] Available:http://jme.endocrinology-journals.org/content/51/2/R51.full
53. Hawkesworth S, Moore SE, Fulford AJC, Barclay GR, Darboe AA, Mark H, et al. Evidence for metabolic endotoxemia in obese and diabetic Gambian women. Nutr Diabetes. Macmillan Publishers Limited; 2013;3:e83. [cited 2015 Sep 25] Available:http://dx.doi.org/10.1038/nutd.2013.24
54. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761–72. [cited 2015 Mar 27] Available:http://diabetes.diabetesjournals.org/content/56/7/1761.long
55. Luche E, Cousin B, Garidou L, Serino M, Waget A, Barreau C, et al. Metabolic endotoxemia directly increases the proliferation of adipocyte precursors at the onset of metabolic diseases through a CD14-dependent mechanism. Mol Metab. 2013;2(3):281–91. [cited 2015 Sep 25] Available:http://www.sciencedirect.com/science/article/pii/S2212877813000598
56. de La Serre CB, de Lartigue G, Raybould HE. Chronic exposure to low dose bacterial lipopolysaccharide inhibits leptin signaling in vagal afferent neurons. Physiol Behav. Elsevier B.V. 2015;139:188–94. Available:http://linkinghub.elsevier.com/retrieve/pii/S0031938414005095
57. de Lartigue G, de La Serre CB, Raybould HE. Vagal afferent neurons in high fat diet-induced obesity; intestinal microflora, gut inflammation and cholecystokinin. Physiol Behav. Elsevier Inc. 2011;105(1):100–5. Available:http://dx.doi.org/10.1016/j.physbeh.2011.02.040
58. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci USA. 2013;110(22):9066–71. Available:http://www.pnas.org/cgi/content/long/110/22/9066
59. Pott J, Hornef M. Innate immune signalling at the intestinal epithelium in homeostasis and disease. EMBO Rep. 2012;13(8):684–98. [cited 2015 Sep 16] Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3410395&tool=pmcentrez&rendertype=abstract
60. Fetissov SO, Hamze Sinno M, Coquerel Q, Do Rego JC, Coëffier M, Gilbert D, et al. Emerging role of autoantibodies against appetite-regulating neuropeptides in eating disorders. Nutrition. 2008;24(9):854–9.
61. Fetissov SO, Sinno MH, Coëffier M, et al. Autoantibodies against appetite-regulating peptide hormones and neuropeptides : Putative modulation by gut microflora. Nutrition. 2008;24:348–59.
62. Thaler JP, Schwartz MW. Minireview: Inflammation and obesity pathogenesis:

The hypothalamus heats up. Endocrinology. The Endocrine Society. 2010;151(9):4109–15.
[cited 2017 Mar 10]
Available:http://www.ncbi.nlm.nih.gov/pubmed/20573720

63. Golay A, Ybarra J. Link between obesity and type 2 diabetes. Best Pract Res Clin Endocrinol Metab. 2005;19(4):649–63.
[cited 2017 Mar 10]
Available:http://www.ncbi.nlm.nih.gov/pubmed/16311223

64. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. The Australian Association of Clinical Biochemists. 2005; 26(2):19–39.
[cited 2017 Mar 9]
Available:http://www.ncbi.nlm.nih.gov/pubmed/16278749

65. Caricilli AM, Saad MJA. The role of gut microbiota on insulin resistance. Nutrients. Multidisciplinary Digital Publishing Institute (MDPI). 2013;5(3):829–51.
[cited 2017 Mar 9]
Available:http://www.ncbi.nlm.nih.gov/pubmed/23482058

66. Mantzoros CS, Liolios AD, Tritos NA, Kaklamani VG, Doulgerakis DE, Griveas I, et al. Circulating insulin concentrations, smoking, and alcohol intake are important independent predictors of leptin in young healthy men. Obes Res. 1998;6(3):179–86.
Available:http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=9618121%5Cnhttp://openurl.ac.uk/athens:lee/?sid=OVID:medline&id=pmid:9618121&id=doi:&issn=1071-7323&isbn=&volume=6&issue=3&spage=179&pages=179-86&date=1998&title=Obesity+Research

67. Müller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, Argente J, et al. Ghrelin. 2015;4:437–60.

68. Queipo-Ortuño MI, Seoane LM, Murri M, Pardo M, Gomez-Zumaquero JM, Cardona F, et al. Gut Microbiota composition in male rat models under different nutritional status and physical activity and its association with serum leptin and ghrelin levels. PLoS One. 2013;8(5).

69. Sanders ME. Probiotics: Definition, sources, selection and uses. Clin Infect Dis. 2008;46(Supplement_2):S58-61-51.
[cited 2014 Dec 29]
Available:http://cid.oxfordjournals.org/content/46/Supplement_2/S58.long

70. Park J, Oh S, Cha Y. Lactobacillus plantarum LG42 isolated from gajami sik-hae decreases body and fat pad weights in diet-induced obese mice. 2013;(Lee 1997).

71. Park DY, Ahn YT, Park SH, Huh CS, Yoo SR, Yu R, et al. Supplementation of Lactobacillus curvatus KY1032 in Diet-Induced Obese Mice is Associated with Gut Microbial Changes and Reduction in Obesity. PLoS One. 2013;8(3).

72. Arora T, Anastasovska J, Gibson G, Tuohy K, Sharma RK, Bell J, et al. Effect of *Lactobacillus acidophilus* NCDC 13 supplementation on the progression of obesity in diet-induced obese mice. Br J Nutr. 2012;108(8):1382–9.
[cited 2015 Sep 6]
Available:http://www.ncbi.nlm.nih.gov/pubmed/22289627

73. Griffiths EA, Duffy LC, Schanbacher FL, Qiao H, Dryja D, Leavens A, et al. *In vivo* effects of bifidobacteria and lactoferrin on gut endotoxin concentration and mucosal immunity in Balb/c mice. Dig Dis Sci. 2004; 49(4):579–89.
[cited 2015 Sep 7]
Available:http://www.ncbi.nlm.nih.gov/pubmed/15185861

74. Wang Z, Xiao G, Yao Y, Guo S, Lu K, Sheng Z. The role of bifidobacteria in gut barrier function after thermal injury in rats. J Trauma. 2006;61(3):650–7.
[cited 2015 Sep 7]
Available:http://www.ncbi.nlm.nih.gov/pubmed/16967002

75. Gauffin Cano P, Santacruz A, Moya Á, Sanz Y. Bacteroides uniformis CECT 7771 ameliorates metabolic and immunological dysfunction in mice with high-fat-diet induced obesity. PLoS One. 2012;7(7).

76. Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM, et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia. 2007;50(11): 2374–83.
[cited 2015 Aug 12]
Available:http://www.ncbi.nlm.nih.gov/pubmed/17823788

77. Cano PG, Santacruz A, Trejo FM, Sanz Y. Bifidobacterium CECT 7765 Improves metabolic and immunological alterations associated with obesity in high-fat diet-fed mice. Obesity (Silver Spring). 2013; 21(11):2310–21.

78. Derrien M, Vaughan EE, Plugge CM, de Vos WM. Akkermansia muciniphila gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. Int J Syst Evol Microbiol. 2004;54(Pt 5):1469–76.
[cited 2015 Sep 6]
Available:http://www.ncbi.nlm.nih.gov/pubmed/15388697
79. Santacruz A, Collado MC, García-Valdés L, Segura MT, Martín-Lagos JA, Anjos T, et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr. 2010;104(1): 83–92.
[cited 2015 Sep 6]
Available:http://www.ncbi.nlm.nih.gov/pubmed/20205964
80. Karlsson CLJ, Onnerfält J, Xu J, Molin G, Ahrné S, Thorngren-Jerneck K. The microbiota of the gut in preschool children with normal and excessive body weight. Obesity (Silver Spring). 2012;20(11):2257–61.
[cited 2015 Jun 25]
Available:http://www.ncbi.nlm.nih.gov/pubmed/22546742
81. Patel S, Goyal A. The current trends and future perspectives of prebiotics research: a review. 3 Biotech. Springer; 2012;2(2):115–25.
[cited 2015 Sep 25]
Available:/pmc/articles/PMC3376865/?report=abstract
82. Lee G-R, Shin MK, Yoon D-J, Kim A-R, Yu R, Park N-H, et al. Topical application of capsaicin reduces visceral adipose fat by affecting adipokine levels in high-fat diet-induced obese mice. Obesity. 2012;21(1): 115–22.
83. Tinkov AA, Nemereshina ON, et al. Plantago maxima leaves extract inhibits adipogenic action of a high-fat diet in female Wistar rats. Eur J Nutr. 2014;831–42.

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