CNS & Neurological Disorders - Drug Targets, 2014, *13*, 305-311

Role of Gut Microbiota in Obesity, Type 2 Diabetes and Alzheimer's Disease

Muhammad I. Naseer[1§], Fehmida Bibi[2§], Mohammed H. Alqahtani[1], Adeel G. Chaudhary[1], Esam I. Azhar[2,3], Mohammad A. Kamal[2] and Muhammad Yasir[*,2,§]

[1]*Center of Excellence in Genomic Medicine Research (CEGMR), King Abdulaziz University, Jeddah, 21589, Saudi Arabia*

[2]*Special Infectious Agents Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia*

[3]*Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, 21589, Saudi Arabia*

Abstract: In recent years, there is a growing interest in research to investigate the importance of gut microbiome in health and diseases. This opens a new area of research for the role of microbial flora of the human gut in inflammation, energy homeostasis, pathogenesis of obesity and other associated disorders. Recent studies propose association of the gut microbiome with development of obesity and metabolic syndromes, such as type 2 diabetes mellitus (T2DM). The T2DM is a metabolic disease that is mainly caused by obesity-linked insulin resistance. The vascular effects of obesity appears to play a role in the development of Alzheimer's disease (AD) that is one of the rapidly growing diseases of a late stage of life all over the world. Studies from both humans and mice models have been demonstrated the engagement of gut microbial flora in the pathogenesis of obesity and host metabolism. The aim of this review is to discuss the current findings that may explain the cascade of gut microbial flora participation in the development of obesity, T2DM and further initiation of AD. In addition, the available data regarding the mechanisms that have been proposed to elucidate the role of gut microbiota in weight gain and possible cause of T2DM and AD have been examined.

Keywords: Gut microbiota, obesity, metabolic disease, type 2 diabetes mellitus, Alzheimer's disease.

INTRODUCTION

Microbes and human health linkage have been identified since the discoveries of Louis Pasteur, Robert Koch, Ilya Mechnikov and other eminent microbiologists of the early nineteen century. However, the host-microbes interactions have been partially unraveled in several parts of the body particularly in the skin, mouth, and gut. Profiling of the gut microbiota from faecal samples by using next generation sequencing of genomic DNA and 16S rRNA gene analysis have shown that the human gut microbiome is a complex and diverse community of 100 trillion bacterial and archaeal cells comprised over 1,000 species [1]. The human microbiome consists of at least 10-fold more cells than exist in the human body [2]. In addition, the human microbiome expresses a large number of genes exceeding the human genome by a magnitude of 150 fold. All these observations support the astonishing concept that we are not 100% human, but a composite of 10% human and 90% microbes [2]. The microbial flora inhabits several parts of the human body such as the respiratory tract, genitourinary tract, surface of skin and mainly in gastrointestinal tract that consists of largest number of microorganisms [3]. The gut microbial flora is important for human health because of nutrient processing, development of the immune system, colonization of antibiotic resistant microbes and stimulation of various other host activities that cannot be performed by our metabolic system alone [4-6]. Recent studies have also revealed the role of gut microbiota in energy homeostasis and fat storage [3, 6, 7]. In particular, recent evidence comes from enhanced production of short-chain fatty acid (SCFA) in a mouse model by *Methanobrevibacter smithii*. The strain is also a predominant archaean in the human gut and suggest that gut microbes may be directly contributing in the development of obesity through increasing the host's energy-harvesting efficiency [5-8].

Obesity is a cause of metabolic diseases such as T2DM, fatty liver, cardiovascular diseases and cancer [5]. T2DM is one of the most common severe metabolic disease that is mainly caused by obesity-linked insulin resistance. In spite of different triggering events, low-grade inflammation with enhance production of inflammatory molecules such as interleukins and tumor necrosis factor alpha (TNF-α) are now considered the pathological hallmarks of obesity and diabetes [9]. Findings from the recent reports based on megtagenomic techniques such as 16S rRNA gene sequencing, fluorescent in situ hybridization and quantitative real time PCR have shown an association of the gut microbiota composition with obesity and diabetes [10, 11]. It has been reported that gut microorganisms increase monosaccharide absorption from the intestinal tract and

*Address correspondence to this author at the King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; Tel: +96626401000/25303; Fax: +96626952076; E-mail: yasirphr@yahoo.com

§These authors made equal contribution to the writing of manuscript.

1996-3181/14 $58.00+.00

instruct the host to enhance hepatic production of triglycerides. This phenomenon is associated with the development of insulin resistance [11, 12]. However, several other factors may also contribute in the development of diabetes such as genetic predisposition, mental stress and infection [12-15].

Obesity is now considered a primary risk factor for development of T2DM and in turn T2DM is a risk factor for the pathogenesis of AD [16, 17]. The adverse effects of obesity on the cardiovascular system have been well studied and suggest that vascular effects of obesity also play a role in the development of AD [18]. Researchers are interested to understand the shared molecular mechanisms in these link metabolic diseases with the intention to lower the risk and severity of AD by treating T2DM. Recent progress in this area of research provides strong support to several mechanisms that could explain the association of these two diseases. Herein, the role of gut microbiome in obesity and associated T2DM linking the continuum of adiposity and T2DM with AD is reviewed. Targeting the association of metabolic diseases may present a unique opportunity for prevention and treatment of AD.

COMPOSITION OF THE HUMAN GUT MICROBIOTA

Gut microbiota of the human is mainly composed of bacteria, archaea, viruses, and some unicellular eukaryotes. This type of flora is associated with every multicellular organism on earth. Microbiota of the human digestive tract comprises of complex and heterogeneous community of over 1,000 species, which reach the concentrations ranging from 10^7 to 10^{12} cells/g intestinal content, from the small intestine to colon based on megtagenomic analysis. The "comprehensive determination of human microbiome composition and the association with host health and disease is one of the key challenges in the 21st century" [19]. Many of the gut microbes stay with their hosts in symbiotic relationships and act together in many physiological processes including immune network activities of the host. However, distribution of the microbial community composition throughout the gastrointestinal tract is not homogenous due to peristalsis and secretions of gastric, bile and pancreatic juice. Diversity of the human gut microbiome is comparatively simple in infants, but becomes more heterogeneous and complex in adults [20]. Lifestyle, diet and environmental factors can also affect the composition and diversity of gut microbial community [21-24]. Taxonomic analysis of 16S rRNA gene sequences have shown that community composition of the gut microbiota is host-specific [21, 25] and relatively stable over time [25, 26]. However, the exact composition of gut microbiota is not fully known due to several limitations of culturing microorganisms from intestinal samples in the laboratory conditions. The recent advances in metagenomic technologies have begun to explore the previously uncultured microbial flora of the human gut [1]. Bacterial flora of the human gut is composed of more than 90% of the species belonging to the phylums *Firmicutes* and *Bacteroidetes*, followed by *Actinobacteria* and *Proteobacteria* [1, 27, 28]. The overall composition of gut microbiota is variable from person to person, but a set of species is conserved and shared between population and may be obligatory for the certain critical functioning of the intestinal tract [1, 29].

INFLUENCE OF GUT MICROBIOTA ON OBESITY DEVELOPMENT

Based on the latest statistics from the World Health Organization, 300 million adults are obese and more than 1 billion are overweight worldwide [30]. Obesity has become a global problem and gut microbiota plays an important role in the pathogenesis of this disease [3]. The exact molecular mechanism that associate gut microbiota with obesity is mainly unclear. However, it has been reported that gut microbiota could contribute to obesity development by influencing different factors such as host genome, inflammation, increased lipoprotein lipase (LPL) activity, lipogenesis, extra calories, increased intestinal permeability, food intake and energy expenditure [3]. Recent report suggests that specific bacterial taxa of the gut microbiota are involved in nutrient uptake and energy homeostasis. While, a lipopolysaccharide (LPS) of bacterial origin derived from gut inhabited microbes may act as a triggering factor and connecting inflammation to the fat-rich diet induced obesity [31].

Previously from Gordon's lab, it was reported that weight status is important in defining gut microbiota composition at the phylum level [23, 24, 29]. The association of high abundance of species from phylum *Firmicutes* and low abundance of *Bacteroidetes* with obesity is concluded by different studies based on animal models and as well as on the human subjects [24, 29]. Animal studies have also shown that gut microbiota composition can be modulated by the host genome. In the genetically obese mice model with mutation in leptin gene contains more species from the phylum *Firmicutes* and fewer *Bacteroidetes* species compared to their lean wild-type mice, even when the mice are fed with the same type of diet [23]. Similar changes in the bacterial species belonged to these groups have also been reported in the gut microbiota of obese humans [24]. The interaction between environment, diet and gut microbes plays an important role in weight gain. It is evident from previous literature that rats susceptible to weight gain have shown ileal inflammation, decreased LPS activity, and increased innate immune system activation as compared to the obesity resistant rats [32]. In both obesity-prone and obesity-resistant rats on the fat-rich diet, there is a decrease of bacterial density whereas Enterobacteriales increased in the obesity-prone rats. Furthermore, an immunoprotein (CD14) which is required to cause an inflammatory reaction to LPS when knockout from mice they become resistant to weight gain [33]. Together the data indicate that rats naturally susceptible to weight gain on a fat-rich diet develop intestinal inflammation. Inflammation in normal rats can cause weight gain, and the absence of inflammation protects rats against weight gain from fat-rich diet [3]. The population of *Bacteroidetes* species increases when weight is reduced, either by carbohydrate or fat-restricted diets, indicates that *Bacteroidetes* are probably active in calories intake [24]. Undigested carbohydrates can be converted into SCFA by the gut microbiota. Higher production of SCFA is directly related to the increased capacity of the ob/ob rate microbiome to harvest dietary energy. In the animal models,

when SCFA are oxidized by the host they can provide additional calories that promotes more fat and weight gain [34].

The microbial flora of intestinal tract is obligatory for digestion of dietary polysaccharides that affects energy harvest from the diet and energy storage in the host [35]. LPL is a key enzyme involved in the release of fatty acids from triglyceride-rich lipoproteins in muscle, heart, and fat. Upregulation of adipocyte LPL activity leads to enhance cellular uptake of fatty acids and adipocyte triglyceride accumulation [35]. Gut microbiota could affect the activity of LPL by influencing the expression of fasting-induced adipocyte factor protein that is over expressed in the germ-free mice and reduce storage of triglycerides in the adipose tissue [35]. Fasting-induced adipose factor (FIAF) is a key inhibitor of LPL activity and plays an important role in preventing obesity. In germ-free mice expression of FIAF is high while inhibition of FIAF expression increases the activity of LPL and storage of triglycerides in adipocytes in the presence of microbiota [35]. Therefore, suppression of intestinal fasting-induced adipocyte factor by microbes promotes adiposity through upregulation of LPL activity in adipocytes and increased hepatic lipogenesis finally enhance accumulation of calories harvested from the diet into fat for storage. This suggests that changes in the intestinal flora composition could be responsible for the development of obesity and diabetes. Therefore, gut microbiota is a key factor in defining host metabolism and energy harvest. Transformation of the gut microbiota either by antibiotics or prebiotics improves metabolic and inflammatory properties, suggesting the importance of gut microbiota in metabolic diseases. For example, modulation of the gut microbial community of obese mice with antibiotics treatment improves glucose metabolism by reducing adiposity and inflammation [11, 36, 37] hence suggesting the involvement of gut microbiota in metabolic and inflammatory diseases.

OBESITY LINKED INFLAMMATION AND DIABETES

Currently, the incidence rate of metabolic disorders is considered a major health issue globally. The pathophysiological mechanisms responsible to develop metabolic disorders in response to obesity are not fully understood. However, in obesity, the over expression of proinflammatory cytokines is evident that develop a status of chronic inflammation. The persistent low-grade inflammation is most probably responsible for the development of obesity related metabolic and inflammatory diseases, such as T2DM [38]. It is also thought that overfeeding is the starting signal of inflammation and studies from both human and mice suggest that adipocytes may acutely evoke the inflammatory pathway in response to this insult [39, 40].

Liver and adipose tissue of the obese individuals compare to lean control exhibit an increased activation of three kinases (c-Jun N-terminal kinase, the inhibitor of the kappa kinase and the protein kinase RNA-activated) that further induce the expression of inflammatory cytokines [41, 42]. In the same metabolic tissues, Toll like receptors and inflammasome of the innate immune system are also activated [43, 44]. In obesity, inflammation results in the inhibition of insulin receptor signaling pathway *via* three kinases described above [45-47]. In patients of T2DM, the expression of pancreatic interleukin-1-receptor antagonist is reduced and interleukin-1 production in Beta cells (β- cells) is induced by high glucose concentrations cause defective insulin secretion, lower cell proliferation and apoptosis. In obese humans, increase circulating level of TNF-α is associated with the evolution of insulin resistance, T2DM, and further associated complications. Therefore, TNF-α is demonstrated to be a link between adiposity and insulin resistance [48].

Recent microbial studies based on 16S rRNA gene sequencing, quantitative real time PCR and fluorescent in situ hybridization have shown a relationship between intestinal microbiota composition and metabolic diseases like obesity and diabetes. For example, *Bifidobacterium* spp. significantly increases in prebiotic treated-mice and correlated with low-grade inflammation and improved glucose-tolerance [36, 49]. Similarly, the development of obesity and diabetes are strongly affected by a fat-enriched diet, which is widely used to induce metabolic diseases. Cani *et al*. [33] proposed that high level of LPS is associated with the development of both obesity and T2DM. Therefore, LPS has the capacity to interfere with both metabolism and the immune system of the host. These observations open a new insight into the role of gut microbiota-derived products and metabolism. Accordingly, it is increasingly documented that the metabolic pathways and the innate immune system are functionally intertwined [50]. Several studies have shown that gut bacteria through modulation of plasma LPS levels can activate the inflammatory processes associated with obesity and insulin resistance [33]. Cani *et al.* [33] have also demonstrated that chronic subcutaneous infusion of LPS significantly produced chronic metabolic endotoxaemia that is able to initiate inflammation and insulin resistance. A high-fat diet has been found to modulate the gut microbial community with a marked reduction in different bacterial groups such as *Bifidobacterium* sp., *Eubacterium rectal, Clostridium coccoides* group and *Bacteroides*-related bacteria [33, 51]. Larsen *et al.* [10], recently characterized gut microbiome in the T2DM patients. The significant reduction in phylum *Firmicutes* and class *Clostridia* was observed in the diabetic group compared to the control subjects [10]. The triggering role of bacterial LPS derived from gut microbes to develop low-grade chronic inflammation, insulin resistance and T2DM was subsequently studied in both genetically and nutritionally obese mice through specific transition of the gut microbiota composition [11, 36]. Changing the gut microbiota of host by antibiotic treatment protects against diet-induced adiposity, oxidative stress, glucose intolerance, insulin resistance and low-grade inflammation [11, 36].

POTENTIAL MECHANISMS LINKING GUT MICROBIOTA TO OBESITY: INITIATION OF DIABETES AND ALZHEIMER'S DISEASE

It is now well established that gut microbiota can influence the central nervous system leading to modulatation of brain function and consequently mood and behavior [52, 53]. Recent studies using germ-free animals exposed to antibiotic, pathogenic or probiotic bacteria have shown that

the post-natal brain development can be influenced by the composition of gut microbiota [54]. It also plays an important role in changing behavior (e.g. anxiety and cognition) and pain responses [52, 53]. Interestingly, gut microbiota of host was found to influence the activity of hypothalamic-pituitary-adrenal axis, which is important for stress responses in later stages of life [54]. There are significant number of evidences to support close interaction between the gut microbiota and immune system. The gut microbiota actively contributes in the development of immune system and interacts with immune cells in the gut to enhance their survival and tolerance. On the other hand, immune cells prevent proliferation of gut microbes into the intestinal epithelia [55]. It can be postulated that gut microbiota has an influence on central nervous system functions *via* immune cells. Cytokines released by immune cells (e.g. microglia and T cells) have crucial roles both in the neuronal plasticity and development of brain [56-58]. Gut microbes may be involved in a number of psychiatric and neurological disorders through their influence on the hypothalamic-pituitary-adrenal axis and interaction with immune system. Recently it was found that germ-free mice were significantly resistant to autoimmune encephalomyelitis in an animal model of multiple sclerosis [59].

Obesity is a potential risk factor for the development of T2DM, hypertension, dyslipidemia, and cardiovascular diseases and in turn diabetes mellitus increases the risk of dementia (vascular and/or neurodegenerative). It has been estimated that T2DM or impairment of glucose metabolism might be present in up to 80% of AD patients [60]. AD is the most common neurodegenerative disease in the elderly population affecting 5% of adults older than 65 years [61]. Neuropathology of AD is characterized by several features including oxidative stress, amyloid deposition, tau phosphorylation, inflammatory processes and extracellular deposition of amyloid beta peptide containing plaques in the cerebral cortex. The presence of neurofibrillary tangles, depletion of mature basal forebrain cholinergic neurons, reductions in cholinergic markers and failure of neuronal cell cycle leading to apoptosis are also prominent features of AD [62-64]. Moreover, in the brain of AD patients many cytotoxic signals especially oxidative stress, inflammation, and iron accumulation can trigger the apoptosis of neuronal cells [65-67].

Previously it was reported that patients with AD are more susceptible to T2DM. In these two diseases, there is possibility of linkage between the process and shared mechanism responsible for the loss of brain cells and β-cells [68]. The islet of Langerhans in T2DM is characterized by the loss of β-cell [69, 70] and islet amyloid polypeptide [71, 72]. This protein is secreted by β-cells and co-expressed with insulin. In AD, brain dysfunction is characterized by loss of neocortical neurons [73] and focal amyloid deposits [74-78]. In several studies, it has been well demonstrated that T2DM increases the risk of developing AD [79-81]. Moreover, up to 80% AD patients have T2DM [82]. Further the roles of T2DM, peripheral insulin resistance, and hyperinsulinemia in relation to cognitive impairment and its progression to AD exploding with new information about the mechanisms of brain insulin resistance, cognitive impairment and neurodegeneration [83-90]. Studies are providing the solid evidence that tau expression and phosphorylation are regulated by insulin and insulin growth factor signaling cascades. The critical aspects of AD can be explained on the basis of impaired insulin signaling [83, 91].

The AD and T2DM share several anomalies such as impaired glucose metabolism and insulin signaling, low grade chronic inflammation and oxidative stress, as well as insulin resistance [92]. Genetic components of the host also involves in development of both AD and T2DM. Incidence rate of these diseases increases with age [93-96]. The patients of T2DM have defective learning and memory functions. The phenomena of hyperglycemia impair cognitive performance is consistent in humans and animals [80, 81, 97, 98]. Generally believed that gut microbiota control obesity that is the cause of T2DM, which consequently causes AD (Fig. **1**). Recent studies have also found the role of gut microbiota in the control of brain function directly by tryptophan metabolism, production of microbial metabolites, microbial neurotransmitters and bacterial cell wall sugars and bile acids [52, 99, 100].

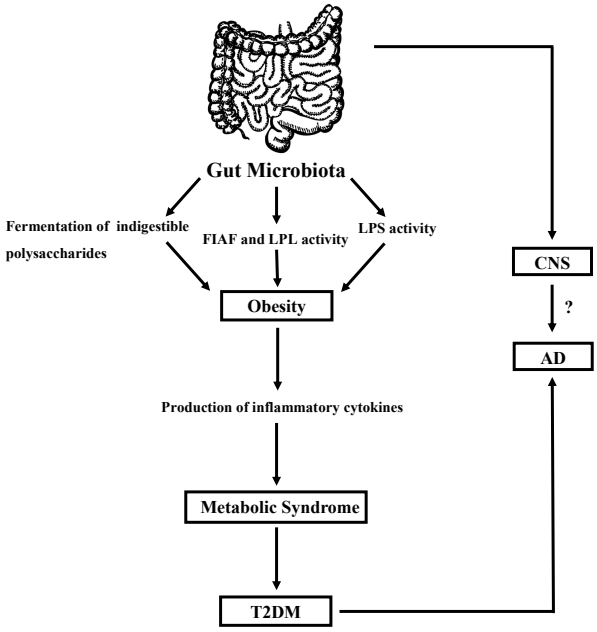

Fig. (1). Mechanism by which intestinal microbiota may contributes to obesity and further development of T2DM and AD. FIAF = fasting-induced adipocyte factor; LPL = lipoprotein lipase; LPS = lipopolysaccharide; T2DM= type 2 diabetes mellitus; AD= Alzheimer's disease; CNS= central nervous system.

Bile acids are steroid acids and synthesized in hepatocytes. Bile acids initially conjugated to an amino acid (glycine or taurine) before the secretion into the gastrointestinal tract [99]. Bile acids inhibit the overgrowth and proliferation of gut's microbes. Bacterial enzymes contribute in transforming primary bile acids to produce secondary bile acids. The secondary bile acids are reabsorbed and returned to the hepatic cells of liver for further processing [99]. Bile acids are also involved in binding and activation of different cellular receptors, such as nuclear receptor farnesoid X receptor and the G protein-coupled receptor TGR5 [100]. Both these receptors play an important role in the modulation of lipid and glucose metabolism in mice. TGR5 signaling in enteroendocrine L-

cells induce secretion of glucagon-like peptide 1, thus enhancing glucose tolerance and improving liver and pancreatic function in obese mice [101]. Therefore, the gut microbiota contributes to the level of obesity and T2DM by controlling lipid and glucose metabolism through bile-acid mediated signaling of these receptors [102]. It can be concluded that bile acids play an essential role in complex signaling and in immune modulation [103].

In addition, the endogenous bile acid, tauroursodeoxy-cholic acid (TUDCA) is a potent neuroprotective agent and acts as a mitochondrial stabilizer and anti-apoptotic agent in several models of neurodegenerative diseases [104]. TUDCA has been shown to be neuroprotective in several models of AD, including amyloid precursor protein and presenilin 1 double-transgenic mice [102]. In Huntington's disease, increased level of TUDCA was also found to be neuroprotective, but still little is known about the role of bile acids in neurodegenerative disease [103]. However, it has been reported that TUDCA is playing a fundamental role to modulate the process of p53-mediated apoptosis in AD [103]. The bile acids, especially glycocholate, glycodeoxycholate and glycochenodeoxycholate have been shown to be altered in plasma profile of AD patients [103]. It has also become evident that microbiota, especially within the gut can greatly influence all aspects of physiology, including obesity, T2DM, gut-brain communication and even behaviour [53].

CONCLUSION

It is evident that gut microbiota maneuver host metabolism and play pivotal role in the pathogenesis of obesity. Several mechanisms that explain the link between gut microbiota and obesity have been proposed especially in animal models. During the past years, a growing body of experimental data and clinical observations support the importance of gut microbiota in the development of obesity and obesity linked metabolic and neurological disorders. The host energy balance and adiposity can be modulated by gut microbiota through different mechanisms e.g., increase energy uptake from the diet, modulation of tissue fatty acid composition, regulation of bile acids and other gut-derived peptide secretion. The role of gut microbiota in sugar and lipid metabolism and in development of LPS induced low grade inflammation in obesity and obesity related T2DM disorder is increasingly recognized. Obesity is considered as a triggering factor for T2DM and in turn T2DM is considered a risk factor for development of AD. Accumulating evidences indicate the importance of gut microbiota as a target for treating metabolic diseases and neurological diseases. However, there is a need of further work to elucidate the possible relationship of gut microbiota with obesity and the mechanisms linking obesity with T2D and AD.

FUTURE PERSPECTIVES

To prevent diseases associated with obesity, use of prebiotics as a supplement diet can be developed as a therapy that stimulates the growth of specific microbes to improve metabolic activity. Future research should focus on delineating the relative contributions of immune, neural and endocrine pathways through which the gut microbiota communicates with the brain to understand the possible link of gut microbiota with AD. A better understanding of these pathways will improve our knowledge about the role of gut microbiota play in a range of neurological disorders, including neuropsychiatric diseases such as pain, depression, anxiety, autism as well as AD. Researchers should focus on gut microbiota for treating metabolic diseases and neurological diseases. Further work is also needed to deeply understand the mechanism that how different bacterial groups can differentially affect central nervous system functioning.

LIST OF ABBREVIATIONS

β-cells	=	Beta cells
FIAF	=	Fasting-induced adipose factor
AD	=	Alzheimer's disease
LPL	=	Lipoprotein lipase
LPS	=	Lipopolysaccharide
SCFA	=	Short-chain fatty acid
T2DM	=	Type 2 diabetes mellitus
TNF- α	=	Tumor necrosis factor alpha
TUDCA	=	Tauroursodeoxycholic acid

CONFLICT OF INTEREST

There is no conflict of interest regarding this article.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the research facility provided by the Center of Excellence in Genomic Medicine Research (CEGMR), King Fahad Medical Research Center KFMRC and DSR under (grant No. HiCi/1432/6-1), King Abdulaziz University Jeddah Saudi Arabia.

REFERENCES

[1] Qin J, Li R, Raes J, *et al*. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010; 464(7285): 59-65.

[2] Savage DC. Microbial ecology of the gastrointestinal tract. Annu Rev Microbiol 1977; 31: 107-33.

[3] Harris K, Kassis A, Major G, Chou CJ. Is the gut microbiota a new factor contributing to obesity and its metabolic disorders? J Obes 2012; 2012: 879151.

[4] Jia W, Li H, Zhao L, Nicholson JK. Gut microbiota: a potential new territory for drug targeting. Nat Rev Drug Discov 2008; 7(2): 123-9.

[5] Esteve E, Ricart W, Fernandez-Real JM. Gut microbiota interactions with obesity, insulin resistance and type 2 diabetes: did gut microbiote co-evolve with insulin resistance? Curr Opin Clin Nutr Metab Care 2011; 14(5): 483-90.

[6] Musso G, Gambino R, Cassader M. Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. Annu Rev Med 2011; 62: 361-80.

[7] Murphy EF, Cotter PD, Healy S, *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.

[8] Samuel BS, Gordon JI. A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. Proc Natl Acad Sci USA 2006; 103(26): 10011-6.

[9] Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol 2004; 25(1): 4-7.

[10] Larsen N, Vogensen FK, van den Berg FW, *et al*. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 2010; 5(2): e9085.

[11] Membrez M, Blancher F, Jaquet M, *et al*. Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice. FASEB J 2008; 22(7): 2416-26.
[12] Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005; 115(5): 1111-9.
[13] Pfeiffer AF. Treat insulin resistance and look out for mental stress. New strategies in the prevention of type 2 diabetes. MMW Fortschr Med 2005; 147(17): 27.
[14] Ma XJ, Jia WP, Hu C, *et al*. Genetic characteristics of familial type 2 diabetes pedigrees: a preliminary analysis of 4468 persons from 715 pedigrees. Zhonghua Yi Xue Za Zhi 2008; 88(36): 2541-3.
[15] Tsukumo DM, Carvalho BM, Carvalho-Filho MA, Saad MJ. Translational research into gut microbiota: new horizons in obesity treatment. Arq Bras Endocrinol Metabol 2009; 53(2): 139-44.
[16] Ahtiluoto S, Polvikoski T, Peltonen M, *et al*. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. Neurology 2010; 75(13): 1195-202.
[17] Schrijvers EM, Witteman JC, Sijbrands EJ, *et al*. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology 2010; 75(22): 1982-7.
[18] Naderali EK, Ratcliffe SH, Dale MC. Obesity and Alzheimer's disease: a link between body weight and cognitive function in old age. Am J Alzheimers Dis Other Demen 2009; 24(6): 445-9.
[19] Sanz Y, Santacruz A, Gauffin P. Gut microbiota in obesity and metabolic disorders. Proc Nutr Soc 2010; 69(3): 434-41.
[20] Fanaro S, Chierici R, Guerrini P, Vigi V. Intestinal microflora in early infancy: composition and development. Acta Paediatr Suppl 2003; 91(441): 48-55.
[21] Dicksved J, Floistrup H, Bergstrom A, *et al*. Molecular fingerprinting of the fecal microbiota of children raised according to different lifestyles. Appl Environ Microbiol 2007; 73(7): 2284-9.
[22] Flint HJ, Duncan SH, Scott KP, Louis P. Interactions and competition within the microbial community of the human colon: links between diet and health. Environ Microbiol 2007; 9(5): 1101-11.
[23] Ley RE, Backhed F, Turnbaugh P, *et al*. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA 2005; 102(31): 11070-5.
[24] Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature 2006; 444(7122): 1022-3.
[25] Jernberg C, Lofmark S, Edlund C, Jansson JK. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. ISME J 2007; 1(1): 56-66.
[26] Zoetendal EG, Akkermans AD, De Vos WM. Temperature gradient gel electrophoresis analysis of 16S rRNA from human fecal samples reveals stable and host-specific communities of active bacteria. Appl Environ Microbiol 1998; 64(10): 3854-9.
[27] Eckburg PB, Bik EM, Bernstein CN, *et al*. Diversity of the human intestinal microbial flora. Science 2005; 308(5728): 1635-8.
[28] Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 2006; 124(4): 837-48.
[29] Turnbaugh PJ, Hamady M, Yatsunenko T, *et al*. A core gut microbiome in obese and lean twins. Nature 2009; 457(7228): 480-4.
[30] WHO: Reducing Risk, Promoting Health Life. Geneva, Switzerland: World Health Organisation; 2002.
[31] DiBaise JK, Zhang H, Crowell MD, *et al*. Gut microbiota and its possible relationship with obesity. Mayo Clin Proc 2008; 83(4): 460-9.
[32] de La Serre CB, Ellis CL, Lee J, *et al*. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. Am J Physiol Gastrointest Liver Physiol 2010; 299(2): G440-8.
[33] Cani PD, Amar J, Iglesias MA, *et al*. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007; 56(7): 1761-72.
[34] Turnbaugh PJ, Ley RE, Mahowald MA, *et al*. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006; 444(7122): 1027-31.
[35] Backhed F, Ding H, Wang T, *et al*. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA 2004; 101(44): 15718-23.
[36] Cani PD, Bibiloni R, Knauf C, *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.
[37] Caesar R, Reigstad CS, Backhed HK, *et al*. Gut-derived lipopolysaccharide augments adipose macrophage accumulation but is not essential for impaired glucose or insulin tolerance in mice. Gut 2012; 61(12): 1701-7.
[38] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993; 259(5091): 87-91.
[39] Watt MJ, Hevener A, Lancaster GI, Febbraio MA. Ciliary neurotrophic factor prevents acute lipid-induced insulin resistance by attenuating ceramide accumulation and phosphorylation of c-Jun N-terminal kinase in peripheral tissues. Endocrinology 2006; 147(5): 2077-85.
[40] Aljada A, Mohanty P, Ghanim H, *et al*. Increase in intranuclear nuclear factor kappaB and decrease in inhibitor kappaB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect. Am J Clin Nutr 2004; 79(4): 682-90.
[41] Solinas G, Karin M. JNK1 and IKK beta: molecular links between obesity and metabolic dysfunction. FASEB J 2010; 24(8): 2596-611.
[42] Nakamura T, Furuhashi M, Li P, *et al*. Double-stranded RNA-dependent protein kinase links pathogen sensing with stress and metabolic homeostasis. Cell 2010; 140(3): 338-48.
[43] Schroder K, Zhou R, Tschopp J. The NLRP3 inflammasome: a sensor for metabolic danger? Science 2010; 327(5963): 296-300.
[44] Song MJ, Kim KH, Yoon JM, Kim JB. Activation of Toll-like receptor 4 is associated with insulin resistance in adipocytes. Biochem Biophys Res Commun: 2006; 346(3): 739-45.
[45] Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci USA 1994; 91(11): 4854-8.
[46] Stephens JM, Lee J, Pilch PF. Tumor necrosis factor-alpha-induced insulin resistance in 3T3-L1 adipocytes is accompanied by a loss of insulin receptor substrate-1 and GLUT4 expression without a loss of insulin receptor-mediated signal transduction. J Biol Chem 1997; 272(2): 971-6.
[47] Boura-Halfon S, Zick Y. Phosphorylation of IRS proteins, insulin action, and insulin resistance. Am J Physiol Endocrinol Metab 2009; 296(4): E581-91.
[48] Wascher TC, Lindeman JH, Sourij H, *et al*. Chronic TNF-alpha neutralization does not improve insulin resistance or endothelial function in "healthy" men with metabolic syndrome. Mol Med 2011; 17(3-4): 189-93.
[49] Cani PD, Possemiers S, Van de Wiele T, *et al*. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut 2009; 58(8): 1091-103.
[50] Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010; 72: 219-46.
[51] Cani PD, Neyrinck AM, Fava F, *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.
[52] Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol 2012; 10(11): 735-42.
[53] Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 2012; 13(10): 701-12.
[54] Sudo N, Chida Y, Aiba Y, *et al*. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol 2004; 558(Pt 1): 263-75.
[55] Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science 2012; 336(6086): 1268-73.
[56] Bhat R, Steinman L. Innate and adaptive autoimmunity directed to the central nervous system. Neuron 2009; 64(1): 123-32.
[57] Boulanger LM. Immune proteins in brain development and synaptic plasticity. Neuron 2009; 64(1): 93-109.
[58] Ros-Bernal F, Hunot S, Herrero MT, *et al*. Microglial glucocorticoid receptors play a pivotal role in regulating dopaminergic neurodegeneration in parkinsonism. Proc Natl Acad Sci USA 2011; 108(16): 6632-7.
[59] Berer K, Mues M, Koutrolos M, *et al*. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature 2011; 479(7374): 538-41.
[60] Tuma I. Diabetes mellitus and dementia. Vnitr Lek 2012; 58(4): 305-8.
[61] Bullock R. Future directions in the treatment of Alzheimer's disease. Expert Opin Investig Drugs 2004; 13(4): 303-14.
[62] Weinreb O, Mandel S, Bar-Am O, Amit T. Iron-chelating backbone coupled with monoamine oxidase inhibitory moiety as novel pluripotential therapeutic agents for Alzheimer's disease: a tribute to Moussa Youdim. J Neural Transm 2011; 118(3): 479-92.

[63] Schliebs R. Basal forebrain cholinergic dysfunction in Alzheimer's disease--interrelationship with beta-amyloid, inflammation and neurotrophin signaling. Neurochem Res 2005; 30(6-7): 895-908.

[64] Selkoe DJ, Schenk D. Alzheimer's disease: molecular understanding predicts amyloid-based therapeutics. Annu Rev Pharmacol Toxicol 2003; 43: 545-84.

[65] Joseph JA, Shukitt-Hale B, Casadesus G, Fisher D. Oxidative stress and inflammation in brain aging: nutritional considerations. Neurochem Res 2005; 30(6-7): 927-35.

[66] Rogers JT, Lahiri DK. Metal and inflammatory targets for Alzheimer's disease. Curr Drug Targets 2004; 5(6): 535-51.

[67] Smith MA, Rottkamp CA, Nunomura A, Raina AK, Perry G. Oxidative stress in Alzheimer's disease. Biochim Biophys Acta 2000; 1502(1): 139-44.

[68] Janson J, Laedtke T, Parisi JE, *et al*. Increased Risk of Type 2 Diabetes in Alzheimer Disease. Am Diab Assoc 2004; 53(2): 474-81.

[69] Westermark P, Wilander E. The influence of amyloid deposits on the islet volume in maturity onset diabetes mellitus. Diabetologia 1978; 15(5): 417-21.

[70] Clark A, Wells CA, Buley ID, *et al*. Islet amyloid, increased A-cells, reduced B-cells and exocrine fibrosis: quantitative changes in the pancreas in type 2 diabetes. Diabetes Res 1988; 9(4): 151-9.

[71] Cooper GJ, Willis AC, Clark A, *et al*. Purification and characterization of a peptide from amyloid-rich pancreases of type 2 diabetic patients. Proc Natl Acad Sci USA 1987; 84(23): 8628-32.

[72] Johnson KH, O'Brien TD, Hayden DW, *et al*. Immunolocalization of islet amyloid polypeptide (IAPP) in pancreatic beta cells by means of peroxidase-antiperoxidase (PAP) and protein A-gold techniques. Am J Pathol 1988; 130(1): 1-8.

[73] Braak H, Braak E. The human entorhinal cortex: normal morphology and lamina-specific pathology in various diseases. Neurosci Res 1992; 15(1-2): 6-31.

[74] Bahmanyar S, Higgins GA, Goldgaber D, *et al*. Localization of amyloid beta protein messenger RNA in brains from patients with Alzheimer's disease. Science 1987; 237(4810): 77-80.

[75] Masters CL, Simms G, Weinman NA, *et al*. Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proc Natl Acad Sci USA 1985; 82(12): 4245-9.

[76] Masters CL, Multhaup G, Simms G, *et al*. Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. EMBO J 1985; 4(11): 2757-63.

[77] Shivers BD, Hilbich C, Multhaup G, *et al*. Alzheimer's disease amyloidogenic glycoprotein: expression pattern in rat brain suggests a role in cell contact. EMBO J 1988; 7(5): 1365-70.

[78] Card JP, Meade RP, Davis LG. Immunocytochemical localization of the precursor protein for beta-amyloid in the rat central nervous system. Neuron 1988; 1(9): 835-46.

[79] Ott A, Stolk RP, van Harskamp F, *et al*. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 1999; 53(9): 1937-42.

[80] Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-analysis. Diab Care 2005; 28(3): 726-35.

[81] Strachan MW, Deary IJ, Ewing FM, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. Diab Care 1997; 20(3): 438-45.

[82] Janson J, Laedtke T, Parisi JE, *et al*. Increased risk of type 2 diabetes in Alzheimer disease. Diabetes 2004; 53(2): 474-81.

[83] de la Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J Alzheimers Dis 2005; 7(1): 45-61.

[84] Steen E, Terry BM, Rivera EJ, *et al*. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimers Dis 2005; 7(1): 63-80.

[85] Lester-Coll N, Rivera EJ, Soscia SJ, *et al*. Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. J Alzheimers Dis 2006; 9(1): 13-33.

[86] Rivera EJ, Goldin A, Fulmer N, *et al*. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis 2005; 8(3): 247-68.

[87] Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol 2004; 490(1-3): 115-25.

[88] Schubert M, Brazil DP, Burks DJ, *et al*. Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. J Neurosci 2003; 23(18): 7084-92.

[89] de la Monte SM, Tong M, Lester-Coll N, Plater M Jr, Wands JR. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. J Alzheimers Dis 2006; 10(1): 89-109.

[90] Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res 2007; 4(2): 147-52.

[91] de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. J Diabetes Sci Technol 2008; 2(6): 1101-13.

[92] Zhao WQ, Townsend M. Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochim Biophys Acta 2009; 1792(5): 482-96.

[93] Newman B, Selby JV, King MC, *et al*. Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. Diabetologia 1987; 30(10): 763-8.

[94] Tanzi RE, St George-Hyslop PH, Haines JL, *et al*. The genetic defect in familial Alzheimer's disease is not tightly linked to the amyloid beta-protein gene. Nature 1987; 329(6135): 156-7.

[95] St George-Hyslop PH, Haines JL, Farrer LA, *et al*. Genetic linkage studies suggest that Alzheimer's disease is not a single homogeneous disorder. Nature 1990; 347(6289): 194-7.

[96] Van Broeckhoven C, Genthe AM, Vandenberghe A, *et al*. Failure of familial Alzheimer's disease to segregate with the A4-amyloid gene in several European families. Nature 1987; 329(6135): 153-5.

[97] Kawasaki F, Matsuda M, Kanda Y, Inoue H, Kaku K. Structural and functional analysis of pancreatic islets preserved by pioglitazone in db/db mice. Am J Physiol Endocrinol Metab 2005; 288(3): E510-8.

[98] Mohapatra J, Sharma M, Singh S, *et al*. Subtherapeutic dose of pioglitazone reduces expression of inflammatory adipokines in db/db mice. Pharmacology 2009; 84(4): 203-10.

[99] Swann JR, Want EJ, Geier FM, *et al*. Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. Proc Natl Acad Sci USA 2010; 108: 4523-30.

[100] Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. Nature 2012; 489(7415): 242-9.

[101] Thomas C, Gioiello A, Noriega L, *et al*. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab 2009; 10(3): 167-77.

[102] Ramalho RM, Nunes AF, Dias RB, *et al*. Tauroursodeoxycholic acid suppresses amyloid betainduced synaptic toxicity *in vitro* and in APP/PS1 mice. Neurobiol Aging 2012; 34(2): 551-61.

[103] Greenberg N, Grassano A, Thambisetty M, Lovestsone S, Legido-Quigley C. A proposed metabolic strategy for monitoring disease progression in Alzheimer's disease. Electrophoresis 2009; 30(7): 1235-9.

[104] Castro-Caldas M, Neves Carvalho A, Rodrigues E, *et al*. Tauroursodeoxycholic acid prevents MPTP-induced dopaminergic cell death in a mouse model of Parkinson's disease. Mol Neurobiol 2012; 46 (2): 475-86.

Received: January 9, 2013 **Revised: March 9, 2013** **Accepted: March 17, 2013**