Journal of Diabetes and Metabolism

Westfall et al., J Diabetes Metab 2015, 6:8
DOI: 10.4172/2155-6156.1000577

Review Article Open Access

The Gut Microflora and its Metabolites Regulate the Molecular Crosstalk between Diabetes and Neurodegeneration

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Abstract

The gut microflora is a community of trillions of bacterial cells synergistically inhabiting the human gastrointestinal tract. These microbes contact everything that is consumed and release regulatory factors that affect host energy homeostasis, lipid and carbohydrate metabolism, activation of immune cells, oxidative state, epithelial cell wall integrity and even neurological signals. The gut microflora is essentially an independent organ supporting human health where imbalances in the gut community populations (dysbiosis) manifest in disease. Diabetes and neurodegenerative disorders such as Alzheimer's and Parkinson's disease share a similar molecular pathology rooted in gut microflora activity. Both of these conditions are associated with a dysbiosis characterized by low species diversity, a higher proportion of pathobionts at the expense of symbionts, an abundance of proinflammatory microbes and fewer butyrate-producing strains. Many of these factors can be ameliorated with *Lactobacillus* spp. and *Bifidobacterium* spp. probiotic treatment aimed to reestablish healthy gut microflora diversity. Indeed, certain commensal and pathogenic strains promote chronic low-grade inflammation that stresses cellular infrastructure eventually leading to apoptosis in both the pancreas and the brain. Also, lack of some beneficial fermentation products such as butyrate and ferulic acid initiates a cascade of events disrupting metabolic homeostasis. Finally, signaling initiated by the microflora and its metabolites has been shown to disrupt the delicate intracellular balance of PI3K/Akt/mTOR signaling, which fundamentally regulates events leading up to diabetes and neurodegenerative disease pathogenesis. The following review investigates the relationship between the manifestation and molecular signaling of diabetes and neurodegenerative disorders and how the balance of gut microflora populations is critical to both prevent and possibly treat these diseases.

Keywords: Diabetes; Alzheimer's disease; Parkinson's disease; Metabolism; Gut microflora; *Lactobacillus*; *Bifidobacterium*; Probiotics; Akt; mTOR

Introduction

Humans coexist with a vast community of microbial species residing in their gastrointestinal tract (GIT) collectively known as the gut microflora. There are an estimated 10^{13}-10^{14} bacterial cells found in the GIT constituting over 1000 species [1,2]. This dense ecosystem constitutes an intimate relationship with the host enabling the digestion of vitamins, minerals and otherwise indigestible fibers while producing signaling factors essential for human health.

The dominant phyla consisting of approximately 90% of the total gut microflora are the Firmicutes and Bacteroidetes, while other significant phyla include Actinobacteria, Proteobacteria, Fusobacteria, Spirochaetae and Verrucomicrobia [3]. The gut microflora significantly varies between people depending on their diet, antibiotic use and other environmental factors although a set of core physiological properties are maintained [4]. Broadly, people can be characterized into one of three enterotypes that are dominated by the genera *Bacteroides*, *Prevotella* or *Ruminococcus* [5]. These enterotypes are age, gender and region independent and seem to depend on the composition of the diet.

Disease is associated with dysbiosis, the imbalance of gut microflora populations. This includes lower species diversity, reduced number of beneficial microbes (symbionts), exaggerated number of harmful microbes (pathobionts), an increase in pro-inflammatory bacteria and a decrease in butyrate-producing bacteria. These changes broadly impact host physiology especially in response to inflammation, oxidative stress, energy homeostasis, hormonal signaling and intracellular signaling cascades therefore contributing to the pathogenesis of many chronic diseases including diabetes and neurodegeneration (Figure 1).

Diabetes is a globally mounting health and economic concern. Diabetes is the most common metabolic disorder worldwide and an estimated 8.3% of the global population is currently living with diabetes. Strikingly, incidence rates are ever rising 3-5% per year [6,7]. This immense rise is not fully explained by genetic and obesity-related variations hence causation must be at least partially attributed to other environmental factors including the progressively degenerating health of the intestinal microflora.

Diabetes is characterized by a dysregulation of insulin activity either by reduced production in the pancreas due to an autoimmune response against insulin producing β-cells (Type-1 diabetes; T1D) or an inappropriate release of insulin in response to glucose levels (Type-2 diabetes; T2D). In either case, insulin desensitization leads to hyperglycemia, a condition that causes severe stress on

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Received April 30, 2015; **Accepted** June 30, 2015; **Published** July 04, 2015

Citation: Westfall S, Lomis N, Singh SP, Dai SY, Prakash S (2015) The Gut Microflora and its Metabolites Regulate the Molecular Crosstalk between Diabetes and Neurodegeneration. J Diabetes Metab 6: 577. doi:10.4172/2155-6156.1000577

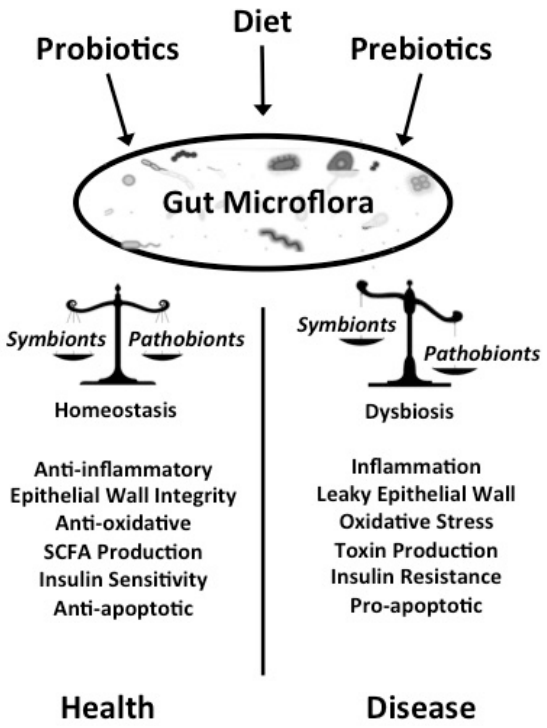

Figure 1: The gut flora has a blanket effect on several aspects of disease development. Diet, probiotics and prebiotics all influence the populations of the gut microflora. Highfat and high-sugar diets negatively impact beneficial microbes leading to dysbiosis characterized by an increase in pathobionts at the expense of symbionts. Probiotics and prebiotics realign gut dysbiosis by promoting a healthy balance of beneficial microbes including butyrate-producing, balancers of energy homeostasis, anti-inflammatory and anti-oxidative species. Since many chronic diseases have a multi-faceted etiology rooted in inflammation and metabolic distress, the broad action of beneficial gut microflora species is a keen target for reversing the pathogenesis of disease.

physiological systems. There are many players contributing to diabetes disease pathology including chronic low-grade inflammation and endotoxemia, oxidative stress, degradation of insulin signaling factors, impaired intestinal permeability and misregulation of intracellular signaling pathways. Notably, all of these pathways are linked to diet-induced dysbiosis [8].

Chronic peripheral hyperinsulinemia and insulin resistance are the two prominent features of diabetes and both these conditions predispose the brain to damage. Under normal conditions, insulin signaling is neuroprotective and protects neurons from various oxidative, inflammatory and toxic stresses. Considering that insulin found in the brain is from pancreatic origin, it is understandable that in a diabetic state, peripheral insulin resistance is carried over to central insulin resistance and resulting impairments in neuronal growth, differentiation, learning, memory and cognition manifest [9-11].

Neurodegeneration is an age-related progressive cognitive decline manifesting in several devastating neurological deficits from motor impairment to memory loss. Like diabetes, inflammation, oxidative stress, energy homeostasis and dysregulation of intracellular signaling pathways constitute the major pathological features of neurodegeneration. Interestingly, there is significant cross-talk between the molecular signaling cascades of neurodegeneration and diabetes, all of which are linked to the health of the gut microflora.

Alzheimer's disease (AD) is characterized by the progressive loss of memory, motivation, disorientation, cognitive abilities and eventually bodily functions. It is the most common neurodegenerative disease, affecting up to 7% of people over 60 and 80% of people over 80 in industrialized countries [12]. Pathologically, AD is characterized by the accumulation of extracellular amyloid plaques and prion-like intracellular neurofibrillary tangles (NFTs) in the brain that are composed of protein aggregates of amyloid(A)β and hyperphosphorylated tau, respectively. Genetic mutations in the amyloid precursor protein (APP) and presenilins (PS) increase the production of Aβ42, a minor form of Aβ that has increased aggregatibility and forms the major part of senile plaques. This plaque accumulation instigates neuronal cell apoptosis from accumulating oxidative stressors and dysregulation of intracellular signaling.

Parkinson's disease (PD) is a multifactorial disease rooted in both environmental and genetic factors and affects 2% of people over 60 and 5% of people over 80, worldwide [13]. It is characterized by the progressive degeneration of dopaminergic neurons in the *substantia nigra*, a midbrain region. The atrophy of these neurons contributes to the progressive motor deficits characteristic of PD including progressive shaking, slowness in movement, rigidity, depression, dementia and digestive difficulties. One of the hallmarks of PD is the formation of Lewy bodies and Lewy neurites, insoluble protein aggregates composed primarily of α-synuclein.

Diabetes and neurodegenerative diseases are inherently distinct pathologies yet frequently manifest together. The decreased insulin levels and corresponding hyperglycemia in diabetes creates various neurological stresses ultimately leading to disease. Patients with T2D have twice the incidence of sporadic AD than healthy individuals [14] and about 40% higher chance of developing PD [15]. In fact, the increased sensitivity of AD patients to insulin and diabetic markers has coined AD as 'Type 3 Diabetes' [16]. This relationship is not surprising as it has been long known that insulin-like signaling (IIS) and metabolic syndrome leads to premature aging and cognitive deficits [17]. PD patients with diabetes acquire more severe disease manifestations [18,19] and it has been shown that 8-30% of PD patients develop diabetes, which is significantly higher than the healthy population, and those people acquire more severe PD symptoms [20]. PD patients also experience a much higher incidence of glucose intolerance and insulin resistance, even without a diagnosis of T2D. In PD, insulin resistance is coupled with an increased vulnerability to chemically-induced neuronal damage, exasperated motor deficits and dopamine depletion indicating that T2D compounds PD symptoms [21].

Relationship between Gut Microflora and the Development of Diabetes and Neurodegeneration

Dysbiosis predisposes, aggravates or even causes diabetes. Diet drastically impacts the composition of the gut microflora evident by the polarity of the diet-dependent enterotypes. This is important as the composition of the gut microflora affects how the body processes energy and extracts calories from food. Likewise, high-fat and high-sugar diets alter the microflora populations such that it provokes the underlying pathology of diabetes, namely imbalances in energy homeostasis, circulating glucose levels, apoptosis, proinflammatory and oxidative states.

In T2D, there is an overall loss of gut microbial diversity with an increase in opportunistic pathogens. This includes a decrease in the phyla Firmicutes with a proportionate increase in Bacteroidetes, together with a decrease in butyrate-producing bacteria [22].

Specifically, *Bacteroides vulgatus, Faecalibacterium prauznitzii* and the *Bifidobacterium* and *Roseburia* genuses are under-represented in diabetic patients [3,23,24]. Various species belonging to the *Lactobacillus* genus are reported to be elevated in diabetic models, however several known probiotic *Lactobacillus* spp. have also been identified as beneficial in treating diabetes (Table 1). In addition, an increase in fecal levels of *Lactobacillus gasseri, Streptococcus mutans* and *Escherichia coli* is predictive of insulin resistance [25]. When insulin-resistant males received lean donor fecal transplantations, there was a significant increase in intestinal microbial diversity and a distinct increase in butyrate-producing bacteria such as *Roseburia* and *Faecalibcaterium* spp. in the feces and *Eubacterium halii* in the small intestine [26]. Not only are gut microbial populations altered in diabetes, but therapeutic interventions to reinstate gut microbial homeostasis has potential to alleviate the associated symptoms.

Certain deficits in beneficial microflora populations are associated with an increased autoimmune response and greater destruction of the insulin producing pancreatic β-cells. It was shown that reduced *Lactobacillus* or *Bifidobacterium* genuses predisposed rat islet cells to autoimmune destruction [27]. Interestingly, an antibiotic

Probiotic	Effects on				References
	Dietary Factors	Insulin Signaling	Inflammation	Molecular Effects	
Phylum Actinobacteria					
Genus *Bifidobacterium*	↓ **HFD** ↓ **Obesity** ↓ **T2D**	↓ **Plasma glucose** ↓ **Insulin resistance** *B. animalis*	**Anti-inflammatory** *B. animalis* *B. brevis* *B. infantis*	↑ **IRS1** ↑ **Akt** ↑ **ERK** ↑ **FA** (*B. animalis*) ↑ **Butyrate** *B. brevis, B. infantis, B. longum*) ↑ **EPAs** (*B. brevis*)	[23,50,205-210]
Phylum Firmicutes					
Genus *Lactobacillus*	↓ **in T2D** *L. reuteri* *L. acidophilus* *L. casei* *L. plantarum* *L. rhamnosus*	↓ **Plasma glucose** *L. reuteri* *L. acidophilus* *L. casei* *L. plantarum* ↓ **Insulin resistance** *L. reuteri* *L. acidophilus* *L. fermentum* *L. casei* *L. plantarum* *L. rhamnosus* ↓ **β-cell injury** *L. plantarum*	**Anti-inflammatory** *L. reuteri* *L. acidophilus* *L. fermentum* *L. casei* *L. salivarius* *L. plantarum* *L. rhamnosus*	↓ **GLP-1** (*L. reuteri*) ↓ **GLP-2** (*L. casei*) ↑ FA (*L. reuteri, L. fermentum*) ↑ **PPARα mRNA** (*L. plantarum*) ↓ **Gluconeogenic genes** (*L. rhamnosus*) ↑ **Lactate** (all spp.)	[22,24,43,44,81,211-224]
Genus *Bacillus*	↑ **T2D** *B. caccae*	↓ **Insulin resistance**	**Anti-inflammatory** *B. caccae* *B mesentericus*		[25,225-227]
Genus *Clostridium*	↓ **T2D** *Clostridium cluster XIV* *Clostridium cluster IV* *Clostridium coccoides* *Clostridium leptum* group ↑ **T2D** *Clostridium difficile*	↓ **Plasma glucose**	**Anti-inflammatory** *C. butricum* **Pro-inflammatory** *C. difficile* *Clostridium cluster XIV*	↑ **Butyrate** *Clostridium cluster XIV*	[25,227-234]
Genus *Faecalibacterium*	↓**T2D** *F. prausnitzii*		**Anti-inflammatory** *F. prausnitzii*	↑ **Butyrate** *Faecalibacterium prausnitzii*	[235]
Genus *Roseburia*	↓**T2D** *Roseburia intestinalis* ↓**T1DM**		**Anti-inflammatory** *Roseburia intestinalis* *Roseburia faecis*	↑ **Butyrate** *R. cecicola, R. intestinalis, R. hominis*	[22,74,235,236]
Genus *Eubacterium*	↓ **T1DM (BBDP mice)** ↓ **T2D** *Eubacterium rectale*	↓ **Insulin resistance** *E. hallii*	**Anti-inflammatory** *Eubacterium rectale*	↑ **Butyrate** *E. rectale, E. ventriosum, E. hallii*	[235]
Genus *Ruminococcus*	↑ **T1DM (BBDP mice)**		**Anti-inflammatory**		[27,235]
Phylum Bacteriodetes					
Genus Bacteroides	↓ **T1DM** ↓ **T2D**	↑ **Circulating Glucose**	**Anti-inflammatory** *B. fragilis*		[27,226,235]
Genus *Prevotella*	↓ **T1DM** ↓ **T2D**		**Anti-inflammatory**	↓ **Mucin**	[22,23,74,229,235,237]
Phylum Proteobacteria					
Genus *Escherichia*	↑ **T2D**	↑ **Insulin resistance**	**Pro-inflammatory** *E. coli k88* **Anti-inflammatory** *E. coli Nissle*		[22,23,74,236,237]

Table 1: The role of gut microflora and their metabolites in diabetes, insulin signaling and inflammation.

therapy regime coupled with a hydrolyzed casein diet prevented islet destruction through mechanisms involving the gut microflora [28]. These studies demonstrate how the gut microflora protect the cellular integrity of pancreatic β-cells, insulin production and the fundamental root of diabetes.

In neurodegenerative diseases, there are similar changes in the gut microflora. Like diabetes, AD and PD are associated with a general loss of microbial diversity [29,30] and shifts in the proportion of the dominant phyla, Firmicutes and Bacteroides. Up to 80% of PD patients suffer from GI dysfunctions linked to poor health of the gut microflora [31] and these GI effects are likely causative to disease development. There is also an overall increase in the pathobionts at the expense of symbionts characterized by an increase in *Proteobacteria* and other pro-inflammatory species with a decrease in *Bifidobacterium* [29,30,32] and *Prevotella* [33]. There have been several studies in germ-free mice investigating the impact of the microflora and specific probiotic treatments on neurological protection in aging. Several *Lactobacillus* (i.e. *L. helveticus, L. rhamnosus, L. fermentum, L. plantarum, L. reuteri, L. acidophilus*) and *Bifidobacterium* (i.e. *B. animalis, B. breve. B.longum*) probiotics that affect inflammatory and oxidative pathways also influence the production of neurotropic factors that ultimately provide protection against the onset of degeneration [34-36].

There are also several species that directly communicate with the vagal afferents in the enteric nervous system to directly effect neuronal activity in the brainstem. *L. reuteri, L. rhamnosus* and *Bacteroides fragilis* all activate vagal afferent signaling [37,38]. This is critical especially for PD development as vagal stimulation in the dorsal motor nucleus of the vagus (DMV) is one of the earliest affected regions for the accumulation of central α-synuclein pathology. Indeed, the microflora-produced metabolites propionate and butyrate also communicate with the brain in a vagal-dependent manner influencing DMV gluconeogenesis, cholinergic neuronal signaling (implicated in AD) and anti-inflammatory pathways [39].

Gut dysbiosis can be ameliorated by prebiotic or probiotic treatment. Prebiotics were shown to increase the level of species in the *Bifidobacterium* genus, an effect that positively correlates with improved glucose-tolerance, glucose-induced insulin secretion and reduced inflammatory markers [40,41]. In a diabetic-prone rat model (BioBreeding diabetes-prone rat; BBDP), transplantation of the probiotic *L. johnsonii* into the host ileum delayed disease progression by regulating the anti-inflammatory Th17 cell response [42]. *L. acidophilus* and *L. casei* probiotic therapy was also shown to elicit concatenate decreases in endotoxemia and oxidative stress markers in a diabetes rat model [43,44]. The potential benefit of probiotic treatment in multi-faceted chronic diseases is immense as several disease pathways are simultaneously affected unlike conventional medicines where only one specific pathway is targeted.

Gut Microflora affects Inflammatory State in Diabetes and Neurodegenerative Disease

Chronic low-grade inflammation and endotoxemia are major causes of age-related diseases and has recently been coined 'inflammaging' [45]. Many inflammatory pathways are dually implicated in both diabetes and neurodegeneration and are rooted in the dysbiosis of the gut [46]. There is ample evidence and several reviews have been written outlining the link of low-grade inflammation to T2D and AD so it will only be briefly outlined below [47,48].

Gut microbes, through lipopolysaccharide (LPS) and other surface signaling molecules, stimulate Toll-like receptors (TLRs) on innate immune cells initiating an inflammatory cascade by the cytokine-promoting actions of NFκB [49]. The high-fat mediated alterations to the gut microflora are correlated with a two-three fold increase in circulating LPS and a state of metabolic endotoxemia [50]. These inflammatory changes are inhibited by both TLR-4 knockout and antibiotic treatment against pro-inflammatory microbes [51] indicating the importance of the gut microflora in instigating diet-induced inflammatory signals. Supporting this, TLR-4 stimulation by Gram-negative bacteria is critical for the development of high-fat diet induced insulin resistance [52] and siRNA-mediated knock-down of TLR-4 suppresses inflammation and insulin resistance triggered by LPS [53,54].

An alteration to the gut microflora by probiotic or prebiotic intervention is linked to reduced gut-induced inflammation. In particular, *Lactobacillus* and *Bifidobacterium* species are known to have potent anti-inflammatory actions (Table 1). *In vitro*, the gut supernatant from *Bifidobacterium infantis* ATCC 15697 was shown to reduce the release of TNFα and increase IL-4 concentrations secreted by macrophages [55]. In addition, there have been many animal and human trials investigating the role of probiotics in reducing inflammatory markers. One famous combinatorial probiotic VSL#3 that contains four strains of *Lactobacilli,* three strains of *Bifidobacteria* and one strain of *Streptococcus* has shown great anti-inflammatory potential [56,57]. Refer to Table 1 for more specific evidence of the anti-inflammatory action of probiotics.

Low-grade chronic systemic inflammation contributes to the development of insulin resistance, diabetes and obesity [58,59]. In both nonobese diabetic (NOD) and BBDP mice, certain probiotic and antibiotic regimes are effective in protecting mice against the onset of diabetes. These changes are correlated with marked changes in the gut microbial communities, partially attributed to the decrease in inflammatory markers [28]. In T2D, the majority of inflammation is derived in the adipose tissue from the activation of immune cells, possibly from the gut microflora. In humans, chronic low-grade endotoxemia increases the adipocyte release of cytokines promoting NFκB expression and insulin resistance [60]. It was later shown that gut-derived inflammation is linked to mechanisms of islet destruction [61]. The actual mechanisms of insulin resistance in the key tissues involved in diabetes (muscle, liver, adipose tissue) remain unknown, but it is certain that these mechanisms interact with inflammatory signaling from diet, obesity and the gut microflora.

To demonstrate the importance of TLR signaling in diabetes, the knock-out of MyD88 (a key intracellular adapter molecules mediating TLR signaling) protected NOD mice from diabetes onset and decreased the autoimmune reaction against pancreatic β-cells in a microbe-dependent manner. Indeed, MyD88 depletion is associated with a lower Firmicutes to Bacteroidetes ratio and an increased proportion of Lactobacilli, Rikenellae and Porphyromonadaeae [62].

There is no mystery that neurodegenerative diseases are highly correlated with systemic inflammation. In the PD brain, aggregation of proinflammatory factors with α-synuclein aggrevates the progression of dopaminergic cell death [63]. Indeed, direct injection of LPS into the brain will destroy dopaminergic neurons implicating a direct role for inflammation in neurodegeneration [64]. Similarly in AD, amyloid plaques activate various caspases and secondary signalers like NFκB and activator protein (AP)-1, which consequently amplify the cytokine proinflammatory response and induce apoptosis [65]. In addition, low-grade inflammation aggravates cognitive impairment

and proinflammatory cytokines co-aggregate with plaques and NFTs further promoting their neurotoxicity [66]. Finally, the neuroprotective ApoE protein is anti-inflammatory and was found to attenuate the Aβ-plaque induced glial activation indicating the importance of mimizing neuroinflammation in the protection against AD [67].

The integrity of the gut intestinal barrier is critical to prevent an unprecedented pro-inflammatory response. Following this, diabetic animals have been shown to have compromised intestinal barrier integrity. In mice fed a high-fat diet, there is a reduction in the expression of tight-junction proteins including occudin and ZO-1 thereby increasing gut wall permeability and circulating LPS levels [50]. In NOD and BBDP mice treated with probiotics, there is an increase in the tight-junction protein claudin coupled with reduced systemic inflammation outlining the importance of gut-derived action on mucosal barrier wall functionality in diabetes associated inflammation [28,42,68]. One study also identified that gut-microflora-mediated epigenetic changes to the TLRs in the gut epithelium could regulate the immune response affecting the diabetic phenotype [69]

Microflora-derived SCFAs Impact Diabetes and Neurodegeneration

Short-chain fatty acids (SCFAs) are the products of gut microbial fermentation of otherwise indigestible fibers. The SCFAs including propionate, acetate and butyrate are pertinent to regulating host energy metabolism, inflammatory state and levels of oxidative stress [70]. Butyrate interacts with the epithelial cells and provides energy whereas propionate and acetate enter the portal venous system and elicit more systemic effects. For example, propionate regulates hepatic lipogenesis and gluconeogenesis where acetate acts as a substrate for cholesterol synthesis [71]. In contrast, butyrate is associated with more anti-inflammatory actions via the inhibition of NFκB [72].

Butyrate

Butyrate preserves the integrity of the intestinal epithelial barrier, which is critical to prevent LPS-containing Gram-negative bacteria from transiting across the epithelial layer and initiating a systemic immune response [70]. To do this, butyrate increases the production of epithelial mucin, enhancing cell wall integrity [46]. Butyrate also activates GPR109A a signaling molecule expressed on the surface of intestinal epithelial cells associated with downregulating NFκB signaling and suppressing TNFα, IL-6 and IL-1β activation [46]. In humans, oral butyrate is beneficial in Crohn's disease and ulcerative colitis indicating its potent anti-inflammatory action in inflammatory conditions [73].

As previously mentioned, diabetic patients have reduced levels Gram-positive butyrate-producing bacteria likely contributing to their disease pathology [74]. In T2D patients, there was a decrease in the butyrate *Clostridiales* bacteria (*Roseburia* and *F. prausnitzii*) with a greater amount of non-butyrate producing *Clostridiales* and pathogens such a *C. clostridioforme* [25]. Indeed, reduced butyrate is associated with endotoxemia, inflammation and the development of insulin resistance in mice [49]. To show this, mice supplemented with oral butyrate have improved insulin sensitivity and an increase in energy expenditure evidenced through improved mitochondrial function [75].

Butyrate also plays a role in protecting against neurodegenerative diseases. The mechanism is not fully elucidated however the histone deacetylase (HDAC) inhibiting activity of butyrate is deemed to be one factor. Recently, HDAC inhibitors have been linked to neuroprotective and neuro-regenerative roles in animal models of neurodegenerative diseases [76]. Indeed, amyloid pathology is correlated to a pronounced dysregulation of histone acetylation in the forebrain of an AD mouse model. Even when administered at a late stage of AD development, sodium butyrate improved memory impairment in these mice [77]. In PD, sodium butyrate was shown to alleviate pre-motor cognitive deficits in a 6-OHDA PD mouse model [78]. In another study, sodium butyrate reduced the degeneration of dopaminergic neurons in a mutant α-synuclein model of PD in *Drosophila melanogaster*. Further, sodium butyrate rescued the motor deficits, early mortality and loss of dopamine expression in the brain of rotenone-treated PD mice [79]. Although not thoroughly researched, the anti-inflammatory action of butyrate would also be protective against both AD and PD.

Ferulic acid

Ferulic acid (FA) is an organic phenolic phytochemical naturally found in coffee, apple seeds, peanuts, rice, wheat and oats. It is also prominent in some Chinese and Indian medicines, namely the Chinese water chestnut (*Eleocharis dulcis*) and hing (*asafoetida*), respectively [80]. FA is a potent free radical scavenger, anti-apoptotic agent and anti-inflammatory agent. From the gut, FA is naturally produced via the intrinsic ferulic acid esterase (FAE) activity of select microbes including various species of *Lactobacillus* [81].

In various diabetes mouse models, FA works via several mechanisms to reduce blood glucose and increase plasma insulin levels [82]. In rats induced with diabetes, FA significantly improved blood glucose levels and oxidative status in the pancreatic tissues [82], to a similar extent as other oral anti-diabetic drugs such as metformin and thiozolidinediones (TDZs) [83]. In leptin deficient *db/db* mice, FA increased plasma insulin, lowered blood glucose, increased hepatic glycogen synthesis and the upregulated the activity of the glucoceogenesis gene glucokinase [84]. FA extracted from Hibiscus leaves prevented insulin resistance by protecting insulin receptor integrity [85]. Applied daily for 8 weeks to Zucker diabetic fatty rats, a model of hyperlipidemia and hyperglycemia, the FA-producing *L. fermentum* reduced fasting insulin levels and insulin resistances indicating that the FA produced from probiotic bacteria is sufficient to improve conditions of diabetes [86].

FA reduces the harsh pro-oxidant conditions of neurodegeneration, diabetes and cardiovascular disease by restoring antioxidant gene and Hsp70 expression [80]. The main targets of FA in preventing oxidative damage include superoxide dismutase (SOD) and catalase (CAT); two enzymes critical to detoxify superoxide anions. In streptozotocin-induced diabetic rats, FA restored SOD and CAT levels in the myocardium and pancreatic tissue [82,87] while simultaneously reducing inflammatory markers and apoptosis in pancreatic β-cells [82]. Interestingly, FA in combination with fish oil was shown to reduce several oxidative markers, improve cognitive state and improve levels of dopamine [88] and other neurotransmitters in a 3-nitropropionic acid model of neurological damage [89].

In the brain, FA provides several neuroprotective effects including anti-inflammatory and anti-oxidant functions [80]. In neurons, FA inhibits peroxyl radical induced apoptosis and at higher doses prevented protein and lipid oxidation [90,91]. Indeed, in a glutamate toxicity model, FA completely inhibited apoptosis and the elevated caspase 3 and reduced Bcl2 levels [92]. In a rat model of cerebral ischemia, FA prevented apoptosis and iNOS induction, indicating that it is protective against external assaults. In aging rats, sodium ferulate supplementation counteracted the age-related increase in pro-inflammatory cytokines [93].

In several contexts, FA has been shown to directly alleviate AD pathology. FA dissolves Aβ plaques therefore preventing its toxicity both *in vitro* and *in vivo* [94,95]. In a transgenic AD mouse model, FA reversed memory deficits, decreased β-amyloid plaque deposits and reduced β-secretase activity and the consequent production of toxic A fragments. Also in this study, FA treatment was associated with attenuated neuroinflammation and reduced oxidative stress [96]. After injection of Aβ, FA treatment ameliorated IL-1β production, neuroinflammation and restored memory loss [94]. Similar anti-inflammatory and Aβ deposition reduction was noted in a transgenic APP/PS mouse model of AD coupled with enhanced cognitive performance [97]. FA was shown to directly inhibit the memory impairment of Aβ1-40 induced AD in rats while reversing the deterioration of anti-oxidative factors. FA also rescued the compromised acetylcholine esterase activity characteristic of the AD phenotype [98]. These effects are likely administered by the combined anti-inflammatory, anti-oxidative and enhanced choline acetyltransferase activity of FA [99].

Heat shock protin (Hsp)70 is a family of chaperone proteins that are strongly upregulated in response to stress and inflammation, which ultimately protect cellular integrity by supporting proper protein folding. In diabetes, the imbalance in the extracellular to intracellular Hsp70 can trigger a proinflammatory state and insulin resistance aggravating T2D development [100]. In neurodegenerative diseases, the accumulation of protein aggregates (Aβ in AD and α-synuclein in PD) is a principle pathology and HSPs have been found to be colocalized to these aggregates. Further, upregulation of Hsp70 (and other chaperones) can trigger the solubilization of protein aggregates both preventing and treating neurotoxicity. Hence, regulation of Hsp70 may be beneficial for both diabetes and neurodegeneration. In this context, FAE was shown to upregulate Hsp70 in rat cortical neurons and prevented ROS and Aβ-induced neurotoxicity [101] indicating the functional ability of FA to regulation Hsp70 levels.

Impact of Insulin, IGF-1 and GLP-1 Signaling in Neurodegenerative Disease

Insulin-like signaling (IIS) promotes many cell-protective and growth promoting pathways. In a healthy state, insulin signaling promotes neurogenesis in the CNS including synaptic maintenance, dendritic sprouting, cell growth, repair and neuroprotection [102,103].

Both the insulin receptor and the IGF-1 receptor, upon being activated by their respective ligand, undergo autophosphorylation and expose docking sites for the insulin receptor substrate (IRS). IRS binding and activation initiates a cascade of phosphorylation events beginning with phosphoinositide 3-kinase (PI3K) and Akt. Akt phosphorylates and largely inactivates its many targets that are proapoptotic (such as GSK3β) and proinflammatory (such as NFκB). Akt also phosphorylates and inactivates the Forkhead box (FOX)O transcription factor that subsequently promotes apoptosis. Finally, Akt also acts on p70s6k, a kinase that feedbacks back onto IRS-1/2 preventing its over-activation. These factors and others will be described in more detail below and how their regulation is important in the mutual regulation of diabetes and neurological disease.

In both PD and AD, fundamental insulin signaling is impaired in the brain exacerbating neurological damage [102]. Cellular insulin signaling impacts numerous molecular cascades affecting apoptosis, production of inflammatory mediators, oxidative damage and others. In particular, there is evidence that insulin signaling directly implicates the specific proteinopathies of PD and AD.

In AD, IlS regulates the metabolism of amyloid β plaques and tau proteins [47,104,105]. There is a strong colocalization of NFTs with the phosphorylated (and inactivated) IRS-1/2 receptors [106] directly associating diabetes pathology with exasperated AD. Also, the levels of phosphorylated IRS at its inhibitory residue are positively correlated with the concentration of Aβ plaques and NFTs and negatively associated with intracellular PI3K and Akt signaling activation [107,108]. The converse is also true, A aggregates have been suggested to trigger the removal of insulin receptors from the plasma membrane in cultured neurons further aggravating AD pathogenesis [109,110].

In PD, reduced IIS suppresses α-synuclein misfolding and neurotoxicity [17]. In the reverse, α-synuclein also interferes with the cytoprotective insulin signaling pathways by inhibiting protein phosphatase 2A activity, which protects insulin signaling. Over-expression of α-synuclein increases IRS-1 phosphorylation, reducing Akt and mTOR signaling, the latter which negatively regulates IRS-1 activity through S6K activity [111]. In the 6-OHDA model of PD in rats, there is severe striatal dopamine depletion manifesting in PD symptoms. In this model, there is a strong depletion of IRS coupled with increased inhibitory phosphorylation of the remaining receptors [112]. Also, silencing of PINK1 and Parkin, two key loss-of-function mutations in familial PD, increases the phosphorylation levels of the IGF-1 receptor impacting the downstream Akt and GSK3β signaling and aggravating PD pathology [113].

Insulin-like growth factor

Insulin-like growth factor (IGF) 1 is a hormone with similar structure to insulin, however IGF signaling leads to fewer metabolic effects and more greatly influences growth and proliferation. IGF release from the liver is controlled primarily by insulin hence IGF is also reduced in patients with diabetes. Activation of the IGF-1 signaling cascade potently induces Akt signaling pathways, a stimulator of cell growth and proliferation (see below). Clearly, reduced levels of IGF-1 signaling in diabetes would have detrimental effects on pancreatic β-cell survival as well as neuronal cell integrity.

Glucagon-like peptide

Glucagon-like peptide (GLP) is secreted primarily from the L-cells in the intestinal epithelial layer in response to dietary factors and indigestible fibers. Gut microbiota fermentation of prebiotics promotes L-cell differentiation in the proximal colon of rats and can upregulate the GLP-1 response up to two-fold in response to a meal in healthy humans [49,114]. Increased levels of *Lactobacillus* and *Bifidobacterium* species in the gut increase the secretion of GLP-1 from the intestinal L-cells in rats, preserve intestinal wall integrity, reduce endotoxemia, improve glucose-stimulated insulin secretion and lower oxidative markers [49,50]. The converse is also true as genetic or pharmacological deletion of GLP-1 prevents the beneficial effects of prebiotics on weight gain, glucose metabolism and inflammatory pathway activation.

GLP is paramount for the incretin effect: the secretion of insulin in response to an oral glucose load. GLPs coordinately induce the glucose-dependent secretion of insulin, suppression of glucagon secretion while in parallel increase insulin sensitivity. In T2D patients, the incretin effect is reduced or even absent. To date, there are several incretin-based therapies (GLP-1 agonists) and the most popular are exenatide and liraglutide [115].

Diabetes-related treatments effective in treatment of neurological disorders

Many therapeutic strategies targeted to control glucose utilization

in T2D also protect against neurological damage in AD and PD [116-119]. For example, nasal application of insulin improved mild cognitive impairment and reinstated the proper Aβ 1-40/1-42 ratio in the CSF of AD patients [120]. The subcutaneous administration of liraglutide, a GLP-1 receptor agonist that improves glucose homeostasis, also ameliorated AD-associated tau hyperphosphorylation in rats with T2D [121,122]. In a model of age-related sporadic AD, liraglutide lead to significant memory retention, prevented the development of phosphorylated tau and Aβ plaques and increased the total hippocampal neuron count indicating that this GLP-1 agonist not only prevents protein aggregates, but targets multiple aspect of AD pathology [123]. Exendin-4 is another GLP-1 agonist and when administered to mice with T2D, significantly reduced tau phosphorylation while upregulating brain IIS [124].

Similar effects were also reported in the 6-OHDA and LPS models of PD. Exendin-4 protected PD mice against loss of dopaminergic neuronal transmission, tyrosine hydroxylase activity and rescued motor function effectively preventing and even reversing the functional impairment in PD [125]. Likewise, in the MPTP toxin model of PD, Exendin-4 protected neurons against degeneration, preserved dopamine levels and improved motor function [126].

The association between therapeutic potential of diabetes and neurodegenerative disease is strong, indicating that there are deeply interconnected molecular signaling pathways between these pathologies. As will be investigated below, many of these pathways are related to the gut microflora and can be ameliorated by correcting dysbiosis in these populations.

PI3K/mTOR/Akt Signaling Intersects Diabetes and Neurodegenerative Disease

The PI3K/Akt/mTor signaling axis is integral to most chronic age-related diseases including diabetes and neurodegeneration. In particular, normal aging critically depends on the tight regulation of these pathways, whose major input is insulin and IGF signaling [108].

Akt

Akt (protein kinase B) is a master regulator pivotal to the signaling network controlling glucose homeostasis, metabolism, apoptosis, cell growth and survival in response to insulin signaling. Deletion of Akt or the PI3K subunit in mice leads to the development of insulin resistance and T2D [127] and hepatic inactivation of these factors is sufficient to produce hyperglycemia and hyperinsulinemia (rev in[128]). Akt phosphorylates AS160 causing it to dissociate from the insulin-responsive isoform of the glucose transporter GLUT4 located in intracellular storage vesicles, which facilitates its exocytosis to the plasma membrane. In this regard, Akt removes glucose from circulation and reduces hyperglycemia [129]. Akt also phosphorylates CRTC2, a CREB co-activator, that increases hepatic gluconeogenesis hence controlling the release of *de novo* glucose into the blood [130]. Akt also instigates a feedback regulation on the IRS. PDK1, the activator of Akt, phosphorylates and activates p70S6k, which consequently phosphorylates IRS inhibiting its activity (Figure 1).

In terms of cell survival, Akt phosphorylation inactivates several proapoptotic proteins including Bad and GSK3β [131]. This pathway is evidenced in models of cerebral ischemia where PI3K/Akt activation suppresses pending neuronal cell death eliciting cell survival [132]. Even in PD, the ratio of active phosphorylated Akt to total Akt is reduced indicating that loss of active Akt leads to cellular degeneration [133].

The gut microflora also plays a role in regulating Akt signaling. The lipoteichoic acid (LTA) cell component on Gram-positive cell walls (similar to LPS on Gram-negative bacteria) activates Akt signaling and consequently downregulates GSK3β [134]. Further, many pathogenic bacteria interact with the Akt/GSK3β pathway to induce inflammation (rev in [135]). More specifically, when mice are fed the prebiotic oligofructose (a known enhancer of *Bifidobacterium* spp. populations), Akt and IRS activity were dually upregulated in a GLP-1-dependent manner [136]. Otherwise, the probiotic *L. rhamnosus* releases several peptides including p75 and p40 that act through the Akt and PI3K pathways to induce growth and cellular proliferation [137]. Finally, *B. breve* binds to immune cells and activates important downstream pathways through the TLR-2 receptor including PI3K and GSK3β [138]. Thus, not only does the gut microflora impact insulin and glucose signaling directly, it also modulates its action downstream by regulating its intracellular signaling.

mTOR

The mammalian target of rapamycin (mTOR) is another signaling hub intersecting diabetes and neurodegeneration. mTOR is a nutrient and energy sensor and broadly affects many biochemical processes including translation, autophagy, transcription, cell growth and lipid synthesis (Figure 1).

mTOR1 is a delicate regulator of glucose metabolism and diabetes development. Molecularly, mTOR is activated by nutrients and growth factors but also through insulin signaling via the PI3K/Akt pathways. mTOR1 phosphorylates and activates S6K1, which regulates insulin signaling via a negative feedback loop involving inhibitory IRS-1 phosphorylation and eventual insulin resistance [139]. Likewise, the sustained activation of mTOR signaling in the AD brain was reported to cause IRS-1 inhibition, disabling normal activation of PI3K/Akt by insulin [140]. In one study, the deletion of S6K improved insulin resistance, enhanced IRS gene expression and prevented diabetes in mice [141]. mTOR1 activity has also been associated with promoting glucose uptake by upregulating GLUT4 expression [142].

mTOR activation through GLP-1 agonists promotes pancreatic β-cell proliferation via S6K activity and prevents neural apoptotic cell loss in T2D [143]. Likewise, rapamycin, the inhibitor of mTOR inhibits β-cell proliferation and induces β-cell apoptosis in obese animals by inhibiting glucose-stimulated insulin secretion [144]. There are some studies in which chronic treatment with rapamycin lead to insulin resistance, glucose intolerance and the development of diabetes [145] and where S6K1 deficient mice became hypersensitive to insulin [146]. This is attributed to the long-term effects of mTOR1 signaling and its effects on β-cell integrity. Chronic mTOR1 activation by glucose impairs IRS signaling which over time induces β-cell insulin resistance ultimately leading to β-cell failure [147,148]. In addition, as insulin signaling itself is a regulator of mTOR1, extensive insulin inhibition with consequently downregulates mTOR, reduces the protective mTOR signaling and insulin resistance featured in T2D [149]. Ultimately, the response to mTOR1 is biphasic: initially mTOR1 increases β-cell production and reduces insulin resistance while over time, chronic mTOR1 activation induces insulin resistance and hyperglycemia ultimately proving toxic to pancreatic β-cells [148].

In the CNS, mTOR plays a critical role in maintaining functionality, plasticity, metabolism and response to stress in post-mitotic neurons [108]. Of particular importance, mTOR is pinnacle in the regulation of proteostasis, the overall folding of cellular proteome, by regulating the balance of translation and autophagy. This regulatory process is key to

prevent the accumulation of toxic protein aggregates such as Aβ in AD and α-synuclein in PD [108,150]. Likewise, hyper phosphorylation and enhanced mTOR activity has been demonstrated in the early stages of AD [151]. Indeed, there are concatenate increases in the downstream factors activated by mTOR including 4EBP, p70S6K and GSK3β, the latter which implements tau phosphorylation and NFT pathology (see below) [152]. In post mortem AD brains, there are also elevated levels of phosphorylated mTOR along with increase expression of its downstream effector, p70S6K [153]. Another study noted that rats induced to have both T2D and AD had significantly higher memory impairment and tau protein hyperphosphorylation than those with either AD or T2D alone. Further, mTOR was reportedly hyperphosphorylated in both groups and it was proposed that the overactivation of mTOR in T2D and the corresponding impaired insulin signaling in the hippocampus increased tau phosphorylation and the prevalence of AD [154].

mTOR plays a similarly important role in PD pathogenesis, however in PD, there is a downregulation of mTOR activity, which leads to oxidative stress, locomotor abnormalities and mitochondrial dysfunctions [155]. Likewise, PD mimetics (6-OHDA, rotenone and MPTP) all reduced mTOR phosphorylation (by reducing Akt activity) while activating apoptotic pathways, an effect rescued with overexpression of mTOR, S6K or 4EBP [156]. Clearly mTOR plays many critical roles in CNS health and maintenance and its regulation remains highly sensitive between promoting healthy and disease states.

Linking mTOR to the microflora it was shown in *Drosophila melanogaster* that one of its commensal bacteria, *Lactobacillus plantarum* was sufficient to reinstate a nutrient-rich signaling environment, even in an actual environment of starvation. This control of hormonal growth signaling upregulated mTOR and Akt signaling thus protecting the flies against aging [157]. It is not surprising that the microflora directly impact mTOR signaling considering that mTOR is a nutrient sensor and the gut microflora control nutrient availability to the host.

FOXO

Forkhead box proteins of the O class (FOXO) are transcription factors that regulate pro-apoptotic genes, proliferation, autophagy, metabolism, inflammation and stress resilience [158]. FOXO inactivation depends on insulin signaling through the PI3K/Akt pathways where phosphorylation of FOXO by Akt relocalizes FOXO from the nucleus to the cytoplasm initiating its degradation. FOXO is an important transcriptional regulator of a conserved insulin response element (IRE: CAAAACAA) present in the promoters of several genes involved in glucose metabolism. These include the two rate-limiting enzymes for gluconeogenesis: phosphoenolpyruvate carboxykinase (Pepck) and glucose-6-phosphatase (G6P) [159]. Indeed, FOXO activation is necessary and sufficient for induction of hyperglycemia following insulin resistance or in T2D (rev in [128]).

FOXO is activated by IlS and many of the longevity-enhancing effects of inhibited IlS is mediated by FOXO [150]. In diabetes, FOXO integrity is required to maintain proper glucose homeostasis and FOXO knockouts protect high-fat fed mice from developing T2D [160]. Notably, mice that overexpress FOXO1 have an impaired ability to regulate blood glucose levels [161]. FOXO also increases the expression of insulin-sensitizing genes, including the peroxisome proliferator-activated receptors or PPARs (see below) [162]. FOXO may transcriptionally repress the PPARγ promoter and possibly even repress PPARγ activity on the protein level [163]. FOXO also negatively regulates mTOR expression through the transcriptional upregulation of glutamine synthetase and AMPK upregulation [164,165].

In normal conditions, FOXO protects cells against oxidative stress and apoptosis [166] including preventing apoptosis in pancreatic β-cells [167]. FOXO transcribes SOD in the mitochondria (MnSOD), CAT and peroxiredoxin III removing superoxide radicals and oxidative stress associated with diabetes and neurodegenerative disease [168]. Under stressful conditions, such as extreme oxidative stress in diabetes or neurodegeneration, FOXO rather promotes cell death and can further increase ROS production [169]. The ability of FOXO to help cells cope with oxidative damage has made FOXO an important protective factor in the development of neurodegenerative disease. Indeed, the age-related FOXO expression has been related to the development of Aβ plaques and AD pathology both through its regulation of oxidative state and even direct regulation of Aβ plaque formation. One of the major mechanisms in the age-related decline of FOXO activity is the corresponding reduction in Hsp70 levels and autophagy, allowing proteotoxicity to grip neurons and lead to apoptosis [170].

Active FOXO creates a proinflammatory environment by transcribing proinflammatory cytokines (IL-1β, TLR4). High glucose, TNF and the LPS found systemically or on the cell walls of Gram-negative bacteria can activate the transcriptional activity of FOXO [169]. In connection to diabetes, LPS inhibits the ability of insulin signaling to inactivate FOXO activity, which may explain the exaggerated inflammatory response coupled with insulin resistance [171,172]. Akt provides an internal negative feedback regulation in FOXO-mediated inflammation. Although LPS increases FOXO activity, LPS also activates Akt, which in turn inhibits FOXO activity limiting its inflammatory action [173]. Also as previously described, mTOR feeds back to inhibit FOXO activation perpetuating the self-limiting inflammatory cycle [165].

In PD, dopaminergic neurons are sensitive to the levels of FOXO. Likewise, in a recent profiling study, FOXO1 expression and its respective transcriptional targets were found upregulated in the prefrontal cortex of PD patients [173]. Constitutive activation of FOXO is proapoptotic while inhibition of FOXO leads to enhanced oxidative damage. However in the context of PD, mild FOXO activity prevented the accumulation of α-synuclein while complete inhibition was shown protective by preventing apoptosis [174]. In fruit flies, expression of the FOXO analog chico reduced lifespan and increased α-synuclein turnover [175]. Further, it was shown that FOXO activation ameliorated PINK1 loss-of-function mitochondrial damage and loss of dopamine in a *Drosophila melanogaster* model of PD indicating its potent neuroprotective effects [176].

Glycogen synthase kinase 3β

GSK3β was originally identified for its ability to inhibit the activity of glycogen synthase and insulin receptors. In response to high levels of circulating glucose, GSK3β phosphorylates and triggers the ubiquitinylation and degradation of IRS1 promoting insulin resistance [177]. It was also found that GSK3β promotes gluconeogenesis in the liver thus aggravating hyperglycemia [178]. In diabetes, GSK3β expression is enhanced exasperating these detrimental effects. Competitive inhibitors of GSK3β increase glucose tolerance in mice as inhibited GSK3β activity should mirror the signaling action of insulin in diabetes by reducing glucose production and enhancing glucose storage. Likewise GSK3β inhibitors have been suggested as therapeutic targets for T2D [179].

Insulin signaling inhibits GSK3β activity through the PI3K/Akt

signaling pathway. In a T2D mouse model, Exendin-4, the GLP-1 agonist, leads to the corresponding rise of PI3K/Akt signaling in the hippocampus and decline of GSK3β indicating the protective effects of GSK3β in diabetes [124]. GSK3β also phosphorylates and inactivates glycogen synthase-2, which reduces glycogen synthesis in muscle. This inhibition also leads to the activation of mTOR and S6K, which promote protein synthesis and cell growth [180].

GSK3β plays a significant role in neuroinflammation and neurodegeneration. GSK3β actually impacts many aspects of neurodegenerative development including inflammation, apoptosis, neurotransmitter receptor signaling, oxidative stress, taupathy, mitochondrial health and more (rev in [181]). In AD, GSK3β activity is significantly increased likely due to the ensuing insulin resistance in the brain [182]. GSK3β is thought to directly promote Aβ production and stimulate the production of NFTs [183,184]. One of the downstream phosphorylation targets of GSK3β is tau, whose hyper-phosphorylation leads to its increased aggregation [106,185]. Indeed, tau protein phosphorylation was reported increased in the brain of T2D rats and effectively reduced after Exendin-4 intervention. This was coupled with a rescued expression of PI3K and Akt and a decline in GSK3β activity indicating that GSK3β plays a role in tau phosphorylation in insulin-resistant brain [124]. Similarly in PD, GSK3β in post-mortem brains is enhanced and also colocalized with Lewy bodies indicating its possible pathological role [185]. In the 6-OHDA and MPTP models of PD, GSK3β is highly elevated and even actively disinhibited through protected phosphorylation events [186-188]. Interestingly, overexpression of α-synuclein corresponds to an increase in GSK3β suggesting that α-synuclein may cause enhanced GSK3β activity [189].

Regulatory action of ferulic acid in PI3K/Akt signaling

FA also imparts regulatory action on the PI3K/Akt and MAPK/ERK signaling pathways [93,190]. The apoptotic activity of FA was completely inhibited in the presence of a PI3K inhibitor indicating that the anti-apoptotic effects of FA depend on the PI3K/Akt pathway. In addition, FA was shown to rescue the level of phosphorylated Akt and the downstream p70S6K in the glutamate toxicity model [92]. In terms of ERK, inhibition of ERK signaling in a model of glutamate toxicity partially abrogated the anti-apoptotic effect of FA [92]. Nevertheless, FA could prevent the decrease of ERK phosphorylation in the glutamate toxicity model, in a MAPK dependent manner [92]. Ultimately, through these pathways, FA effectively inhibits apoptosis activity by inhibiting caspase 3 activation and PARP cleavage.

In another model, middle cerebral artery occlusion (MCAO), rats who simultaneously received FA did not experience a decrease in the levels of phosphorylated Akt or elevated GSK3β and FA further attenuated the increase in phosphorylated CRMP-2 indicating that FA should indeed elicit an effect on Akt, ultimately affecting the GSK3β/CRMP signaling pathway [129]. In the same model, it was also shown that FA rescued the attenuated levels of mTOR, p70S6K and S6 phorphorylation levels describing its neuroprotective role [191]. Finally, another study confirmed that FA attenuated the ischemic injury-induced inactivation of PI3K and Akt signaling thereby promoting neuronal survival via its anti-apoptotic actions on Bad expression [191].

Peroxisome proliferator-activated receptors

PPARs are a family of three nuclear receptors PPARα, β/δ, γ that are highly expressed in metabolically active tissues. In response to a series of signaling ligands, their role is to regulate lipid metabolism, glucose homeostasis and enhance the action of insulin [192]. Due to their metabolic actions PPARs are intimately involved in the pathology of both diabetes and neurological disease.

One of the main ligands of PPARs are the essential fatty acids. Intriguingly, the gut microflora plays a prominent role in synthesizing and regulating fatty acids. In particular, the *Bacteroidetes* and *Firmicutes* phyla synthesize isomers of conjugated linoleic acid, a substrate of PPARs that erects anti-inflammatory action [193,194]. The probiotic *Bifidobacterium breve* is particularly efficient in this effect. Feeding *B. breve* to mice and pigs, there was not only significantly higher levels of EPA and DHA, but a reduction in inflammatory mediators, again possibly regulated through PPAR signaling [195].

Thiazolidinediones (TZDs), including rosiglitazone, are PPARγ agonists and many varieties are currently used as anti-diabetic drugs as they reduce insulin resistance and blood glucose levels in patients with T2D [196]. Interestingly, patients receiving such drugs were also protected from neurodegenerative pathologies. Indeed, PPARγ agonists promote neuronal development, protect cells from toxicity against various stresses and even protect neurons from Aβ toxicity and the accumulation of NFTs ultimately protecting the host from cognitive degeneration (rev in [197]). The PPARγ agonist LSN862 were also shown to be protective against dopaminergic degeneration and inflammatory markers in the MPTP-model of PD [198]. Despite the abundance of clinical evidence, the precise mechanism PPARγ agonists' action remains to be fully elucidated. PPARγ agonists are potent anti-inflammatory and anti-oxidant agents thus contribute to the joint action on both diabetes and neurodegeneration. Also, PPARγ agonists intersect with the PI3K/Akt/TOR and MAPK/ERK signaling pathways to affect the underlying pathology of disease development (Figure 2). TZDs increase Akt phosphorylation and activation in a PI3K dependent manner [199]. TZDs also inhibit GSK3β thus providing neuroprotection by reducing the risk of apoptosis. In addition, TZDs increase the phosphorylation of ERK1/2 two-fold and the neuroprotective action was shown to be conducted in a MAPK-dependent manner [200].

PPARs do induce the transcription of PTEN, an inhibitor of Akt activation. Albeit contradictory to the previous discussion on diabetic and neurodegenerative protective effects of Akt activation, this inhibitory effect in dependent on cell type [199] hence may not affect signaling in neither the pancreas nor in neurons. In fact, one PPARγ agonist even decreased the ischemia-reprofusion elevated of PTEN levels in neurons indicating a more complex regulatory scheme [201].

PPARγ activity is directly regulated by the gut microflora. Species in the *Bacteroides* genus targets RelA, an NFκB subunit for cytoplasmic redistribution. PPARγ is also relocated along with it as PPARγ is found in complex with nuclear RelA and goes forth to promote anti-inflammatory actions [202]. Post-transcriptionally, *Enterococcus faecalis* regulates PPARγ activity through phosphorylation resulting in its enhanced, yet transient, transcriptional activation [203]. Indirectly, SCFAs such as butyrate produced from the gut microflora activate PPARγ enhancing its beneficial effects on glucose homeostasis and anti-inflammatory potential [204].

Conclusion

Chronic diseases including diabetes, AD and PD have an integrated and multifaceted etiology coupled with prominent imbalances in the gut microflora communities. Despite distinct disease characteristics, diabetes and neurodegenerative disorders are often found comorbid and even aggravate the other's severity linking each of these disorders to a common source. Hence, similarities in the kind of gut microflora

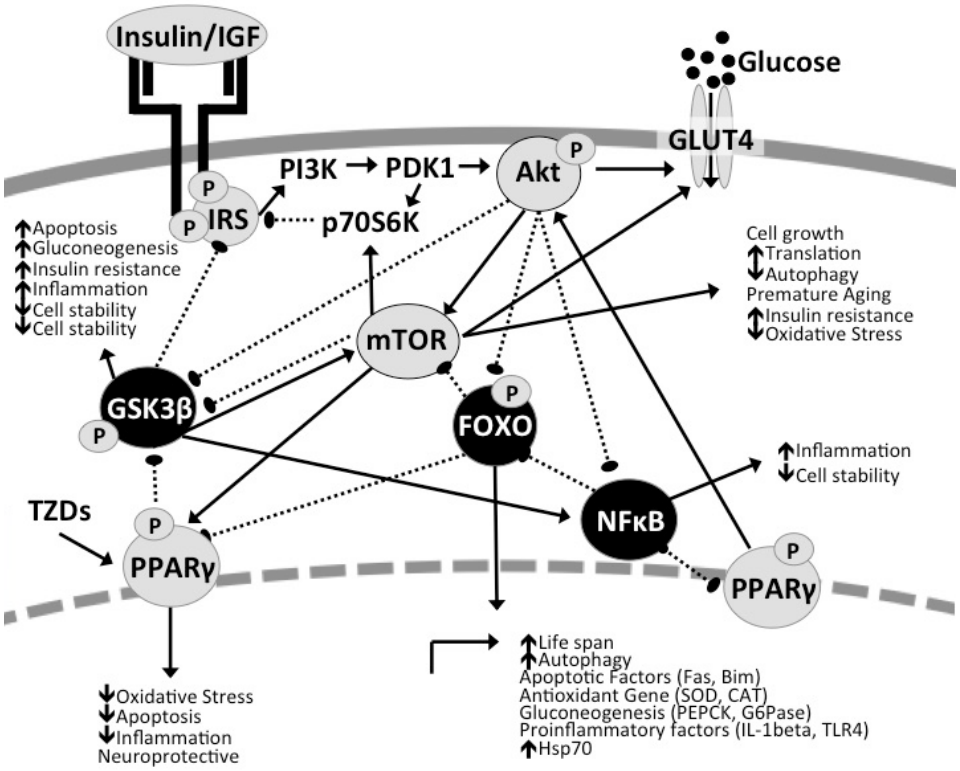

Figure 2: The interactions of intracellular signaling pathways implicated in diabetes and neurodegeneration. Insulin signaling initiates a series of protective intracellular signaling cascades that regulate systemic metabolic state, protect cells from apoptosis and reduce inflammation. In diabetes and neurodegenerative disease, reduced insulin signaling reduces activation of Akt and mTOR resulting in cell-destructive fate. Light grey shaded factors are generally regarded as neuroprotective or beneficial to maintaining cellular health and are upregulated in response to insulin signaling. Black-shaded factors are generally regarded as destructive and normally kept at low expression by normal insulin signaling. IGF = insulin-like growth factor; IRS = insulin receptor substrate; GLUT4 = glucose transporter 4; PI3K = phosphoinositide-3 kinase; PDK1 = phosphoinositidedependent kinase; Akt = protein kinase B; p70S6K = ribosomal protein S6 kinase; Mtor = mammalian target of rapamycin; GSK3β = glucagon synthase kinase 3 beta; PPARβ = peroxisome proliferator-activated receptor gamma; TZD = Thiozolidinedione; FOXO = Forkhead box 'O' type.

dysbiosis and correlated root causes like inflammation, metabolic stress and disrupted intracellular signaling indicate that maintaining a healthy gut environment is essential to prevent, treat and possibly reverse chronic disease. Probiotic and prebiotic treatment eradicate gastrointestinal dysbiosis and can ameliorate inflammatory, metabolic and molecular imbalances ultimately preventing or treating diabetes and neurodegenerative disease development. This opens the potential for new therapeutic approaches that incorporate gut microflora-modifying agents like probiotics to simultaneously treat several aspects of these complex disease pathologies. In particular, fermentation products including butyrate and ferulic acid have broad effects on inflammatory, oxidative and PI3K/Akt/mTOR signaling pathways therefore treatment with probiotics known to secrete these metabolites would benefit disease outcome.

Probiotics have vast potential for use in diabetes and other metabolic diseases as probiotics simultaneously target multiple aspects of the disease pathology. Through the mechanisms described above, probiotic therapies reduce insulin sensitivity, inflammation, oxidative stress and gastrointestinal distress thus ameliorating all major aspects of diabetic etiology. On the other hand, modern therapies including Metformin, Thiazolidinediones and GPL-1 agonists only affect insulin sensitivity or the secretion of insulin. The scope of these therapies is limited as they only influence the final manifestation of diabetes (insulin sensitivity) and do not address the underlying cause or the compounding action of inflammation, oxidative stress and gastrointestinal imbalances in diabetic patients. Hence, probiotics provide and novel and promising approach over conventional therapies to mitigate diverse aspects of diabetes possibly preventing or reversing the development of diabetes.

Acknowledgments

The authors would like to thank National Sciences and Engineering Research Committee (NSERC) for funding this research.

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