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Review article

Sugar in mind: Untangling a sweet and sour relationship beyond type 2 diabetes

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ABSTRACT

It is widely recognised that type 2 diabetes (T2D) represents a major disease burden but it is only recently that its role in neurodegeneration has attracted more attention. This research has shown that T2D is associated with impaired cerebral health, cognitive decline and dementia. However, the impact on the brain of progressive metabolic changes associated with the pre-clinical development of the disease is less clear. The aim of this review is to comprehensively summarise how the emergence of risk factors and co-morbid conditions linked to the development of T2D impact cerebral health. Particular attention is directed at characterising how normal but elevated blood glucose levels in individuals without T2D contribute to neurodegenerative processes, and how the main risk factors for T2D including obesity, physical activity and diet modulate these effects. Where available, evidence from the animal and human literature is contrasted, and sex differences in risk and outcomes are highlighted.

1. Introduction

It is now widely accepted that type 2 diabetes (T2D) is associated with impaired cerebral health and cognitive decline. A large number of studies have shown that individuals suffering from T2D have higher levels of cerebro-vascular disease, smaller total and regional brain volumes, decreased cerebral connectivity, increased beta amyloid deposition and tau phosphoralisation, accelerated rates of cognitive decline, and are at greater risk of developing dementia (Adams, 2013). What is less clear is when, before the onset of T2D, these pathological processes start developing, to what extent they are linked to variation in blood glucose within the normal range in those without T2D or its pre-clinical stage, and what are the main determinants of variability in blood glucose levels in generally healthy individuals. The purpose of this review is thus to examine factors associated with normal blood glucose variability in individuals without T2D, and to contrast them with those demonstrated in individuals with T2D, to discuss the biological mechanisms implicated in these effects and how they may lead to neurodegeneration and impaired cognition, and to identify gaps in our understanding to guide future research.

In the following sections evidence from animal and human research will be carefully presented. Research demonstrating the involvement of major factors in the modulation of blood glucose levels will be critically reviewed with a particular focus on modifiable lifestyle and environmental factors. Findings reporting associations or causal links between blood glucose variability, cerebral health, and cognitive function will be scrutinised. And importantly, particular care will be taken in discussing plausible biological mechanisms linking risk factors (e.g. obesity, diet, exercise) and impaired brain and cognitive function.

While this review will focus more prominently on findings across the whole available literature, samples studied vary greatly in their cultural, socio-demographic, health and lifestyle characteristics, making generalisation difficult. Consequently, in this review we will also make regular reference to findings established in a single well-characterised normative population cohort, the PATH Through Life Study (PATH) (Anstey et al., 2012), on which we collaborate (see frame for study description). This will allow us to summarise the effects that can be detected concurrently in a homogenous group of individuals living in the community in a specified cultural context (see also Fig. 1 at the end of this review which contrasts findings from the broader literature from those from the PATH study).

The PATH study

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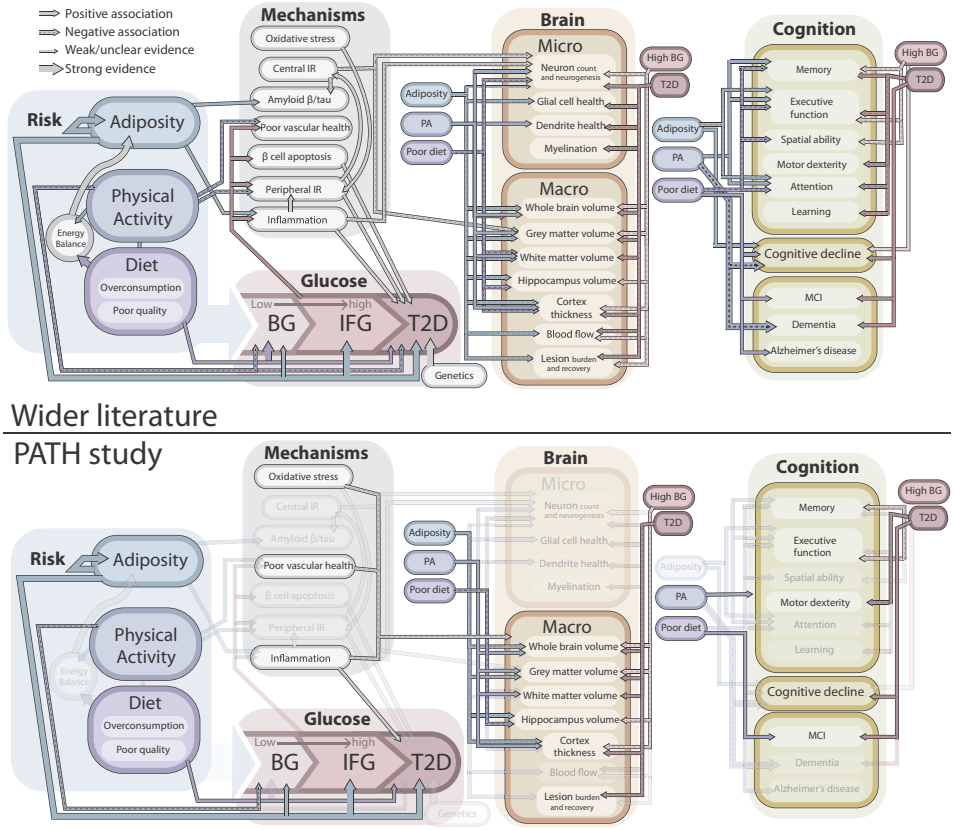

Fig. 1. Overview of current evidence linking blood glucose and type 2 diabetes to brain and cognitive outcomes.

The Personality & Total Health (PATH) Through Life project (Anstey et al., 2012) is a large population-based longitudinal cohort study investigating ageing, health, cognition and other individual characteristics across the lifespan. Aged 20–24, 40–44 and 60–64 years at baseline (1999–2001), 7484 participants were selected at random from the electoral rolls of the three federal electorates that make up the Australian Capital Territory and the neighboring town, Queanbeyan. Follow-up occurred at four year intervals over twelve years. Four waves are complete to date. Follow-up participation rates have been high; 90% of the full 7484 at baseline at wave 2, 81% at wave 3, and 63% at wave 4. At baseline, 51% of participants were female. Though this varies somewhat depending on individual studies selection criteria, PATH publications have a well-balanced sex ratio.

All participants provided information on a broad range of fixed and time-varying individual characteristics in interviews. Several sub-studies with more specific data collection were also carried out, notably the Magnetic Resonance Imaging (MRI) sub-study, and the Health and Memory sub-study, which focused on individuals from the oldest cohort who performed particularly poorly on selected cognitive tests. Both of these studies involved repeated MRI and venous blood measures in the 40 s and 60 s cohorts.

Finally, although this review is not intended to systematically describe all aspects of the clinical development and presentation of T2D we will first briefly summarise the main mechanisms implicated in glucose homeostasis and the typical characteristics of the disease to provide a broader context to the present review.

2. Type 2 diabetes (T2D)

Diabetes mellitus or type 2 diabetes is a metabolic disease which affects an estimated 400 million people worldwide (Ogurtsova et al., 2015). Historically, it has mainly developed in adults, particularly from midlife onwards but recently it has become more common in adolescents and children (Pinhas-Hamiel and Zeitler, 2005). By 2030 it is predicted that more than 10% of all adults will suffer from T2D (Ogurtsova et al., 2015).

2.1. Genetic and environmental risk factors

The single most predictive factor of T2D is being overweight or obese (Chen et al., 2011), particularly in early adulthood (before 40 years). Other major T2D modifiable risk factors include physical inactivity, diet, smoking, hypertension, and inflammation. Age, sex, family history and ethnic background are the main non-modifiable risk factors. T2D incidence tends to occur earlier in life in men, and lifetime prevalence is slightly higher in women (Kautzky-Willer et al., 2016), possibly due to greater longevity in women (Gale and Gillespie, 2001). The lifetime risk of developing T2D in an individual with both parents suffering from T2D is 70%, and 40% if only one parent is affected (Prasad and Groop, 2015). Twin studies have shown that over long follow-ups the heritability of T2D is high, but this substantially varies. Concordance in mono-zygotic twins ranges between 30% to over 80% (van Tilburg et al., 2001), and in di-zygotic twins around 40%. This suggests a substantial environmental component. Once diagnosed, the impacts of T2D can be successfully managed through lifestyle, pharmacological, and dietary interventions targeted at managing healthier glucose levels, but currently the condition cannot be cured due to the largely irreversible physiological changes underlying the chronic increase of blood glucose levels.

2.2. Peripheral and central glucose homeostasis mechanisms

In healthy individuals heightened blood glucose levels after a meal lead to insulin secretion by pancreatic β-cells into the blood stream. In turn, the secreted insulin binds to insulin receptors in sensitive tissues and leads to intra-cellular glucose uptake. Tissues most sensitive to insulin binding include the liver, pancreas, fat, and muscle with substantial binding occurring also in parts of the brain and the gastrointestinal tract (Watanabe et al., 1998). In contrast, decreased blood glucose levels lead to secretion of glucagon by pancreatic α-cells, which

stimulates the release of newly synthesised glucose into the blood stream. Blood glucose homeostasis is also controlled centrally, predominantly by the hypothalamus, in response to leptin and insulin signalling (Tups et al., 2017). Leptin is secreted by adipose tissue as a proportion of body fat stores and, in normal weight individuals, suppresses appetite and is associated with decreased food intake and increased weight loss. Beyond energy intake, leptin also regulates glucose levels through a more acute response which involves increasing sensitivity of hypothalamic neurons to insulin as well as other pathways (Koch et al., 2010). Insulin, aside from its peripheral effects, is also implicated in glucose homeostasis through central mechanisms. Insulin has been shown to activate some hypothalamic neurons thus leading to suppression of hepatic glucose production through vagal innervation. Although, as noted above this action is dependent on sensitisation of thalamic neurons by leptin. Finally, glucose sensing neurons have been identified in the brain, principally in the hypothalamus, and are thought to also contribute to systemic and central glucose homeostasis through complex molecular pathways and regulation of the activity of the sympathetic and *para*-sympathetic branches of the autonomic nervous system (Tups et al., 2017).

2.3. Impaired glucose homeostasis and T2D disease progression

Pre-diabetes is characterised by a progressive decrease in sensitivity of insulin receptors (insulin resistance, IR) and a concurrent increase in blood glucose levels. Initially, blood glucose is maintained at normal levels through an increase in insulin production and release. However, increasingly stressed β-cells progressively fail to respond to glucose sensing mechanisms which leads to lower insulin secretion and, over time, to β-cell apoptosis. The processes involved in the development of IR and decreased insulin production are complex and include many metabolic pathways within β-cells and in target tissues and particularly fat and muscle (Fröjdö et al., 2009; Cerf, 2013). However, inflammation and oxidative stress are thought to be the main mechanisms leading to IR, through impairment of intra-cellular pathways, and to insulin deficiency through damage to β-cells structure.

While peripheral mechanisms have historically been thought to be the main contributors to the development of T2D, recently, the contribution of central processes has been acknowledged (Tups et al., 2017). While these mechanisms are complex and not fully understood the available evidence suggests that, somewhat similar to insulin resistance, excess body fat promotes heightened leptin production in obesity, which in turn leads to inflammation and the development of leptin insensitivity/resistance in thalamic neurons. This in turn impairs glucose homeostasis by reducing central insulin action and down-regulation of hepatic glucose production, as well as through non-insulin dependent pathways. Similar effects are also thought to impair central sensing of glucose levels and related regulating mechanisms.

Chronically elevated blood glucose levels promote a persistent state of low-grade systemic inflammation and a variety of intra-cellular metabolic disturbances in different tissue types which over time lead to the development of atherosclerosis, small vessel disease (affecting particularly the kidneys and the brain), and peripheral neuropathies. The progressive development of these co-morbidities and the onset of IR starts well before the onset of T2D proper. While a clinical diagnosis of T2D is defined as a fasting blood glucose (FBG) level ≥126 mg/dl (7 mmol/l) or a glucose level of ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT), it is preceded by pre-clinical stages of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (American Diabetes Association, 2004). IGT affects approximately 7% of all adults (Ogurtsova et al., 2015) and is defined as having a FBG level of between 140 and 199 mg/dl (7.8–11 mmol/l) in an OGTT. IFG is defined as a FBG level between 100 and 125 mg/dl (5.6–6.9 mmol/l) and affects 5–17% of children and adolescents with obesity, and between 20 and 35% of all adults (Liu et al., 2014; Chen and Yeh, 2013; Karve and Hayward, 2010). There is also evidence that, as with T2D, IFG prevalence is higher in men in midlife (41–64 years), but higher in women in older age (65 years +) (Chen and Yeh, 2013).

2.4. Section summary

There are a substantial, increasing number of people with T2D worldwide. While heritability and twin studies indicate a genetic component, the likelihood of developing diabetes is closely tied to environmental and modifiable risk factors, the most predictive of which is being overweight or obese. The development of T2D is underpinned by irreversible physiological changes accompanying the chronic increase of blood glucose levels: decrease in insulin sensitivity, and insulin deficiency arising from β-cell apoptosis.

3. Blood glucose within the normal range

Fasting blood glucose levels are considered within the normal range according to the American Diabetes Association if they are ≤100 mg/dl (5.6 mmol/l). Although most research in this field has been directed at pre- and clinical T2D, recently it has become clearer that variability in FBG within the normal range is clinically significant. In the PATH study, we were amongst the first to show that FBG in the high end of the accepted normal range was associated with increased brain atrophy in a structure, the hippocampus, essential to normal memory function and highly relevant to cognitive decline and dementia (Cherbuin et al., 2012). We have since noted chronically elevated FBG levels within the high end of the accepted normal range are also associated with accelerated cortical thinning (Shaw et al., 2017), grey matter atrophy (Walsh et al., 2017), and decreased cognitive performance (Mortby et al., 2013). Others have also shown associations between chronically elevated FBG levels, accelerated brain atrophy in ageing (Enzinger et al., 2005), and poorer memory and executive functioning (Messier et al., 2003).

These associations are unsurprising because the thresholds for IFG and IGT are somewhat arbitrary. The remainder of this review will explore how some determinants of overweight/obesity and T2D lead to an increase in FBG levels (Fig. 2), and how this increase, even within the normal (albeit elevated) range, has a negative impact on cerebral and cognitive health (Figs. 3–5). The effects of elevated FBG will be contrasted to those of pre- and clinical T2D.

4. Adiposity and blood glucose

Approximately 30% of the world adult population is overweight or obese (World Health Organisation, 2015). In developed countries the proportion is much higher and ranges from 45% in Eastern

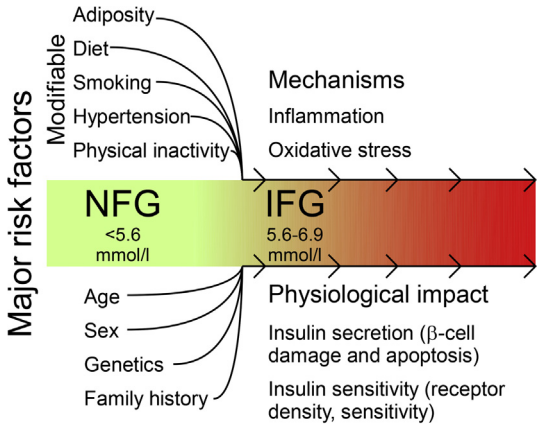

Fig. 2. Major risk factors, pathological mechanisms, and their impact on blood glucose metabolism. *Note.* Figure depicts a schematic overview of the major modifiable and non-modifiable risk factors and impaired glucose metabolism.

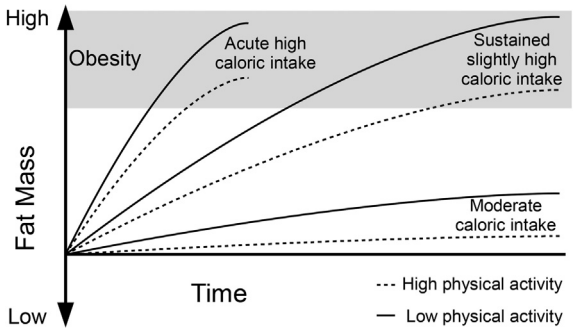

Fig. 3. Relationship between body mass, caloric intake, and physical activity over time. *Note.* This conceptual schematic depicts differing trajectories of body mass over time, contingent on differing levels and durations of caloric intake and amount of physical activity. Note that while physical activity (dotted vs dashed line) has some impact on body mass, caloric intake (three groupings of lines) has a more pronounced association with body mass index.

Mediterranean countries to 50–60% in Europe and the Americas (Yatsuya et al., 2014). Of critical importance, obesity is a strong predictor of future obesity (Simmonds et al., 2016). As in adults, almost all child cases of T2D are attributable to the "paediatric obesity epidemic" (Ludwig and Ebbeling, 2001). Children with obesity are at a five-fold risk of being obese in adulthood, and 70% of adolescents with obesity remain obese until after the age of 30 (Simmonds et al., 2016). In the PATH study, obesity in mid- and late life typically increases with as few as 4% of participants exhibiting stable weight or weight loss (Walsh et al., 2018). Surprisingly, the association between body mass index (BMI; normal: 18.5–24.9; overweight: 25–29.9; obese: 30 +) and FBG has not been extensively or systematically reported in the literature.

The available evidence suggests that it is modulated by age and sex. There is no clear association between BMI (standardized for age and sex) and FBG in children (Mehdad et al., 2012). In contrast, in generally healthy young adults correlations ranging from 0.38 (24.5 years, 40% female) (Innocent et al., 2013) to 0.40 (18–22 years, 44% female) (Farah et al., 2015) have been reported (without adjustment) and suggest that the relationship may be stronger in females. In midlife adults (40 years, 53% female) a correlation of 0.25 after adjustment for age has been reported which differs little between sexes or ethnicity (White/African American) (Shen et al., 2006). In the PATH study, we found that in participants spanning mid-life to old age (aged 45–78 years, 50% female) every one BMI point increase above 25 (lower bound of overweight range) there was an approximate 0.05 mmol/l increase in FBG. Thus, an individual with moderate obesity (BMI 35) would be predicted to have a blood glucose 0.75 mmol/l higher than an individual with normal weight which is substantial as it represents almost 30% of the normal range (3–5.6 mmol/l). This association varied substantially across individuals due to the individual-level complex interplay between glucose, BMI, and factors such as physical activity (Walsh et al., 2018), and the longitudinal context, such as whether the individual was in the process of stably gaining, loosing, or maintaining BMI (Walsh et al., 2018). Overall, the available evidence suggests that increasing adiposity is associated with FBG and that this association appears to increase with age, particularly in women, although research to date has not fully accounted for shared effects with co-morbid conditions.

4.1. Section summary

The research to date suggests that adiposity is positively associated with fasting glucose, and that this association becomes more pronounced in later life. However, more research is required to disentangle the association between adiposity and FBG due to the likely impact of co-morbid conditions.

5. Diet, physical activity and adiposity

Diet and physical activity are the main determinants of adiposity. However, in order to better understand the links between behaviours and pathology it is not only important to identify risk factors but also to consider the potency and time course of their effect. Therefore, this section will summarise the magnitude and characteristics of the associations between diet, physical activity and adiposity.

5.1. Diet and adiposity

Several aspects of diet influence body weight and increase in fat mass, with caloric intake and diet quality being the main contributors. While short-term variability in caloric intake appears to have relatively little impact on body weight, an imbalance between the amount of energy consumed and expended over longer periods (on the order of years) leads to weight gain (Hall et al., 2011; Hill et al., 2012; Wiklund, 2016). This relationship is complex, non-linear, and modulated by many factors including age, sex, level of physical activity to name a few, so is best explored by focussing on an individual. As an example based on validated NIH modelling (Hall et al., 2011), an adult male aged 30 years in an office job (sitting most of the day) who exercises moderately (walking, cycling once a week) and of ideal weight (e.g. ~66 kg) for average height (175 cm, BMI 21.5) would become overweight (BMI ≥ 25, kg) within 3 years if he consumed only 12% excess energy (2880 kcal/day instead of the recommended 2580 kcal/day). For a woman using similar assumptions (average height 162 cm, 56.5 kg) the excess energy required to reach overweight (65.6 kg)

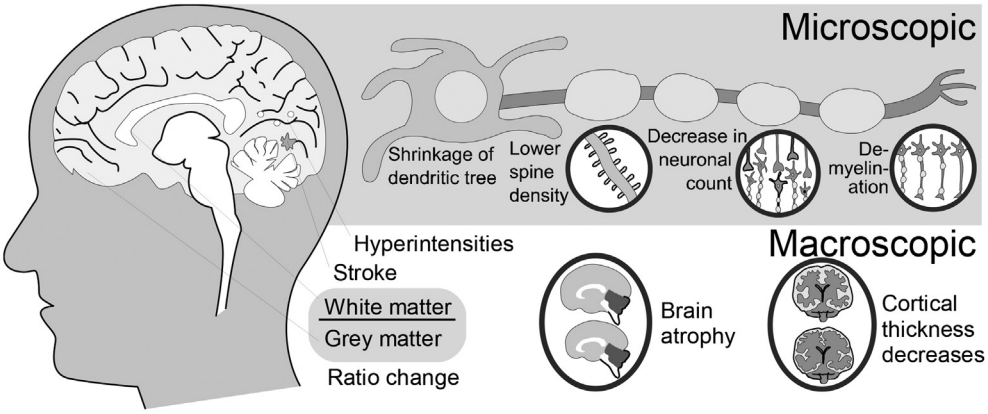

Fig. 4. Impact of high blood glucose and type 2 diabetes on the brain *Note.* This conceptual diagram summarises the key impacts of high blood glucose and type 2 diabetes on the human brain.

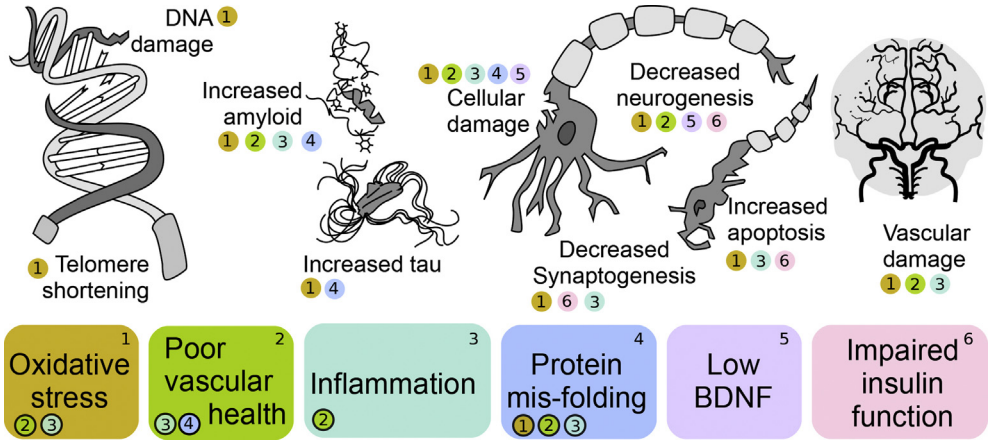

Fig. 5. The impact and interplay between mechanisms underlying the detrimental impact of high blood glucose and type 2 diabetes on the brain *Note.* Numbers and colours denote associations between biological mechanisms (listed across the bottom of the figure) and specific impacts (depicted by images and titles across the top of the figure).

would also be ~12% above recommended energy intake (2280 kcal/day vs 2030 kcal/day). Given a can of cola or a full milk latte contain ~150 kcal each and a typical burger with fries ~500 kcal this scenario is a realistic reflection of how small but sustained excess caloric intake is likely to lead to weight gain.

Diet quality is also important. Poorer diet quality is associated with weight gain, and becoming overweight or obese in adults and children (Aljadani et al., 2015; Hu et al., 2016), with a stronger association in men than women. Poor diet quality is jointly associated with both higher BMI and insulin resistance, further emphasising the close link between energy balance and glucose metabolism (Langsetmo et al., 2016). However it should be noted these findings are significantly influenced by the type of instrument used to assess diet (Asghari et al., 2017). It is also noteworthy that the effect of diet on weight gain appear to be mediated at least in part by central mechanisms. In animal models, high-fat diet is associated with inflammation in the hypothalamus which is detectable as early as 1 day after the start of high-fat feeding (Thaler et al., 2012) and may be a causative mechanism underlying the development of obesity by promoting insulin and leptin insensitivity (Tups et al., 2017).

5.2. Physical activity and adiposity

The relationship between physical activity and adiposity is complex and not fully understood. Physical activity directly influences the energy balance between intake and expenditure. While it appears that physical activity has decreased by around 100 kcal/day in the last 50 years, dietary energy intake has increased by 500 kcal/day, an amount of energy equivalent to a typical burger and fries, between the 1970s and 2000s (Wiklund, 2016). In a population of young US adults (21–35 years) the threshold to achieve energy balance was estimated at 7116 steps/day (Shook et al., 2015). This suggests that physical activity may not play the most central role in the energy imbalance, and concomitant increased obesity prevalence observed in the population. Nevertheless, physical activity modulates adipose tissue metabolism beyond increased energy expenditure through potent biological mechanisms including oxidative stress, inflammation, cardio-vascular health, and modulation of food appetite. Nevertheless, those who exercise more are more likely to maintain a normal weight or to gain less weight, as demonstrated in both large population samples and twin studies with twins who have discordant levels of physical activity (Ball et al., 2001; Schmitz et al., 2000; Leskinen and Kujala, 2015; Leskinen et al., 2005).

5.2.1. Section summary

Diet, physical activity and adiposity contribute together to energy balance. Overall, the evidence indicates that sustained excess energy intake is the primary driver of overweight and obesity, and accordingly that diet quality and quantity has a greater impact on adiposity than physical activity. Nonetheless, physical activity is associated with immediate and prospective benefits in weight maintenance.

6. Diet, physical activity and blood glucose

Since dietary intake, and insufficient physical activity are the main determinants of adiposity, they are also associated with blood glucose levels before the clinical emergence of T2D. If salient, this would support the view that pathological processes leading to T2D follow a slow gradual progression, and that between-individual variability in blood glucose levels even within the higher end of the normal FBG range are clinically meaningful. Therefore, this section will summarise the magnitude and characteristics of the associations found between diet, physical activity and elevated FBG at the higher end of the accepted normal range and in T2D.

6.1. Diet and blood glucose

There is a clear association between diet and short-term blood glucose levels. Intake of foods with higher glycaemic indexes (GI; e.g. simple sugars, refined foods, fats) lead to higher blood sugar levels than low GI foods in randomised controlled trials both in healthy individuals and in people with diabetes (Kaur et al., 2015; Kaur et al., 2016; Augustin et al., 2015). Similar findings were also reported for foods containing less fibre, more proteins, more saturated fats, as well as foods containing lower beneficial phytochemicals typically found in nuts, berries, chocolate and tea/coffee (Russell et al., 2016). Importantly, these effects have been demonstrated to have a long lasting impact with diets of poorer quality and higher GI leading to poorer glucose control and higher risk of insulin resistance and T2D over time (Russell et al., 2016; Nansel et al., 2016). Our own research in the older cohort of the PATH study (n = 208, aged 60–65, 48% female) showed that, although poorer quality diets are generally associated with higher energy intake, the association between poor diet quality, elevated glucose levels, and risk of incident T2D remains significant when total energy intake is taken into account (Walsh et al., 2017). This is important because it supports the notion of a central effect of diet quality whereby, as noted above, diets high in saturated fats and low in antioxidant contribute to thalamic inflammation, central insulin and leptin resistance, and lead to impaired glucose homeostasis and higher FBG (Tups et al., 2017).

6.2. Physical activity and blood glucose

In children, objectively measured physical activity has been found to be associated with insulin resistance at age 8 and 12 years, although not with fasting blood glucose levels (Huus et al., 2016). The same

pattern of low physical activity resulting in obesity and T2D is seen in children, however the thresholds of the activity required vary substantially throughout childhood due to rapid physical growth (Ebbeling et al., 2002). Large systematic reviews in adults shows similar associations (Way et al., 2016; Yates et al., 2015; Yu et al., 2015). In addition, a study of generally healthy twins (50–74 years) who had been discordant for physical activity for at least 32 years showed that the more active twin had on average a fasting blood glucose levels 0.5 mmol/l lower than the less active twin (average difference in physical activity between twins ~ 35 MET/hour/week) (Leskinen et al., 2013). Consistent with these findings, lack of physical activity in a large cohort (n = 28,946) was associated with a 29% increased risk of having T2D, while a recent *meta*-analysis found that those who exercised 150 min/week (11.25 MET/hour/week) were at a 26% decreased risk of incident T2D (Smith et al., 2016). While the impact of physical activity on adiposity is less pronounced than that of diet, longitudinal evaluation of the older cohorts of the PATH study (n = 716, 50% female) suggested the most sedentary individuals (undertaking < 16.5 MET/hour/week, falling short of WHO recommendations for an ideal 20–30 METs/week) may experience a 1 mmol/L higher FBG compared with their more active contemporaries over three years (Walsh et al., 2018).

6.3. Section summary

Both diet and physical activity have an impact on pre-clinical FBG levels, and subsequent T2D incidence. Even when total energy intake is taken into account, poor quality and high GI diet are predictive of incident T2D. Physical activity above approximately 11 MET/hour/week has a protective effect.

7. Blood glucose and brain

Strong evidence showing an association between the clinical development of T2D and impairment of brain structure and function is available. It would therefore be expected that the early stages of the pathological processes leading to T2D (i.e., elevated blood glucose levels, insulin resistance, impaired fasting glucose), as well as T2D's main risk factors (i.e. obesity, diet, sedentary lifestyle) would also be linked to poorer cerebral health. In this section, we will review the microscopic and macroscopic changes in brain structure and function attributable to T2D's pathological progression while attempting to separate those differences clearly present in the clinical stages from those linked to the development of risk factors and the pre-clinical symptomatology.

Animal models of T2D

The goal of animal models is to parallel T2D in humans via the disruption of insulin metabolism, presence of hyperglycemia, and often (but not always) co-morbid factors including obesity and cardiovascular disease. T2D animal models can be grouped in three broad categories including genetic, chemically-induced, diet induced or a combination of these. Rodent models are most widely used due to their shorter lifespan, ease of genetic manipulation, and easy housing. Although, larger mammals whose physiopathology is more closely related to that of humans have also been studied (Bellinger et al., 2006; De Koning et al., 1993; Henson and O'Brien, 2006; Wagner et al., 2006).

Genetic models have been used to explore beta cell function, beta cell survival, and the effects of hyperglycaemia (Cefalu, 2006; Špolcová et al., 2014; Yamauchi et al., 2002). A major limitation of these models is that it is not clear whether the genetic variations underlying them and the associated phenotype is comparable to the human physiopathology of T2D. Although at least for the most commonly used genetic models which involves impaired leptin signaling, over-eating and subsequent obesity, a common disease pathway shared with the human form of the disease is clearly identified (Cefalu, 2006; Lönnqvist et al., 1995).

T2D can also be induced via diet, chemicals, or a combination of both. High fat feeding, where dietary calories from fat is raised from the typical ~10% to ~60% or over, mirrors the pathway of weight gain, decreased beta cell function, and impaired glucose tolerance seen in humans (Cefalu, 2006). Dietary manipulation is effective in inducing obesity and insulin resistance in animal models prone to weight gain, but in many instances simultaneous genetic or chemical manipulation is required. For example, the same high-fat diet produces clearer hyperglycaemic effects in C57BL/6J mice than A/J mice (Surwit et al., 1988), and low-dose streptozotocin in combination with a high fat and simple carbohydrate diet produces clearer diabetes-like complications than high fat diet alone (Surwit et al., 1988) (see (Tripathi and Verma, 2014) for a review).

It is important to note that some animal models involve marked sex differences in diabetogenic responses (King, 2012), and it is common for animal studies to be constrained to a single sex, most often, male. Consequently, it is particularly important to consider the implications of these methodological approaches when evaluating the animal evidence aimed at shedding light on the effects of abnormal glucose metabolism.

7.1. Microscopic brain changes

Animal models of T2D have demonstrated the emergence of a number of consistent cellular changes in neurons and glial cells (Ho et al., 2013). Compared to wild type rats, animals genetically prone to developing T2D have been found to have fewer neurons (~11%, male sample only) (Hussain et al., 2014). Although glial count does not appear to differ between T2D and wild type animals, significant glial activation has been demonstrated in T2D indicating increased pro-inflammatory activity. Decreased number of neurons in T2D is also consistent with insulin's neuroprotective action. Insulin has been shown to be anti-apoptotic and protective against oxidative stress (OS) and amyloid beta toxicity in neurons (Ball et al., 2001; Schmitz et al., 2000). Therefore, decreased insulin levels and decreased neuronal insulin sensitivity are expected to lead to increased neurodegeneration. This is demonstrated in untreated male diabetic rats who underwent an acute hyperinsulinemic severe hypoglycemic clamp and who experienced a 15-fold increase in brain damage compared to normal rats (Reno et al., 2013). However, diabetic rats that were intensively treated and had nearly normalised glucose levels experienced markedly reduced neuronal damage. It should also be noted that microscopic changes in T2D are not limited to neurons or the central nervous system. In male rats, Barrière et al. demonstrated the presence of increased demyelination in peripheral nerves which is consistent with the development of diabetic peripheral neuropathy in the later stages of the disease (Barrière et al., 2018).

Impaired neuronal structure and function has also been reported in T2D. Compared to controls, synaptic count and dendritic arborisation has been found to be significantly lower in a male rodent models of T2D (Ramos-Rodriguez et al., 2017; Lietzau et al., 2016; Wang et al., 2014). Importantly, these effects were shown to become stronger in a dose-effect manner as the disease progressed, indicating they start developing in the context of elevated glucose levels. Moreover, when T2D mice were inter-bred with mice prone to developing Alzheimer's pathology their synaptic density was further decreased, particularly close to amyloid plaques (Ramos-Rodriguez et al., 2017).

Very few histopathological studies have investigated microscopic brain changes in humans with T2D (Nelson et al., 2009). Most post-mortem studies have been conducted on peripheral nerves and ganglia, as well as on the retina. They demonstrated the presence of enlarged dystrophic axons in the periphery, and fewer glia with smaller processes in the retina in T2D (Lechner et al., 2017; Schroer et al., 1992). Surprisingly, no corresponding studies targeting the central nervous system (CNS) could be identified, and of the available CNS histological investigations, it would appear that the research focus has been exclusively on small vessel disease, micro-infarcts and related pathology which have all been found to be more prevalent in T2D (Nelson et al., 2009).

Some converging evidence is however available from histological studies investigating neuropathology in obesity. In animal experiments (primarily in males), obesity is associated with increased intra-cellular tau phosphorylation in neurons (Gratuze et al., 2013; Spolcova et al.,

2014) (precursor to the development of neurofibrillary tangles in AD), decreased dendritic spines numbers, and differences in microglia morphology (Hao et al., 2016; Bocarsly et al., 2015). In humans, the histological evidence is very limited and contradictory. One study found a lower neuronal counts in the frontal and temporal cortices of individuals with overweight/obesity (n = 16, 31% female) (Gómez-Apo et al., 2017). However, another could not detect any difference (n = 17, 1 female), although greater variability in neuron numbers was detected in participants with obesity (Weise et al., 2015).

Physical activity has a positive impact on the brain microstructure. Animals who undertake voluntary or guided exercise experience greater neurogenesis, increased spine density and mitochondria number, and larger dendritic trees in the medial temporal and frontal cortices as well as in the cerebellum (Stranahan et al., 2007; Dietrich et al., 2008; Gonzalez-Burgos et al., 2011). Importantly, in a mice model of T2D in which a decrease in hippocampal dendritic spine density was observed, the implementation of a caloric restriction diet and voluntary exercise on a running wheel led to an increase in spine density (Stranahan et al., 2009). This suggests that some of the microscopic brain changes associated with T2D can be at least in part reversed through dietary and exercise interventions.

The extent to which variability in blood glucose levels in the absence of T2D impact the brain microstructure is less clear. Some evidence suggestive of an effect has been demonstrated in the context of a caloric restriction diet. Male mice undergoing such a diet have lower blood glucose levels (~20–30%) than mice eating ad libitum, with this effect persisting into old age (Guo et al., 2015). Moreover, male mice on a caloric restriction diet have been found to have better white matter fibre integrity as assessed by diffusion tensor imaging (DTI), and increased neurogenesis (Guo et al., 2015; Lee et al., 2002). Consistent findings were also reported in humans. For example, in the Framingham Heart Study (n = 4095; 19–72 years) increasing fasting blood glucose levels were associated with a lower measure of integrity in white matter tracts (fractional anisotropy) (Weinstein et al., 2015). While it is possible that these findings were in part driven by participants with T2D, it is unlikely to be limited to this group since they only composed 3% of this sample.

7.2. Macroscopic brain changes

7.2.1. T2D

There is extensive evidence of macroscopic differences associated with T2D. In animal models, volumetric differences have been identified for the frontal cortex, hypothalamus and hippocampus, with cortical volumes decreasing by approximately 19% following streptozotocin-induction of T2D in rats (Wang et al., 2014). These volumetric differences are linked to inflammatory pathways, and related increase vulnerability to cerebro-vascular damage; hypoinsulinemic diabetes in APP/PS1-STZ mouse models is associated with an increase in toxic Aβ, phosphorilated-tau, systemic low-grade inflammation, and higher rate of spontaneous haemorrhaging in the brain (Baluchnejadmojarad et al., 2017). Interestingly, there is some animal evidence that pre-clinical high FBG can also have macroscopic impacts on brain volume; hyperglycaemia is associated with accelerated cerebral atrophy in grey mouse lemurs (Djelti et al., 2017), insulin insensitivity is associated with lower frontal grey matter volume in rhesus monkeys (Willette et al., 2012).

Similar differences have been reported in humans. T2D-related atrophy has been mainly found in relation to cortical and sub-cortical grey matter, but some findings are also available for global cerebral and white matter atrophy, as well as sulcal widening (van Harten et al., 2006). A recent systematic review and *meta*-analysis of existing studies found that on average T2D was associated with 2% lower brain volumes (Zhang et al., 2019). However, there was an insufficient number of longitudinal studies to determine conclusively whether the annual rate of global or regional atrophy was greater in T2D. Importantly, another study (Bryan et al., 2014) (n = 614) surveying exclusively T2D patients found that disease duration was associated with grey matter atrophy with every additional 10 years in duration being associated with a 1% decrease in total grey matter volume. Similar findings were reported by Saczynski et al. (n = 489) not only for grey matter but also for white matter, white matter lesions, and infarcts volumes (Saczynski et al., 2009) as well as by Tiehuis et al. (n = 151) for total brain atrophy (Tiehuis et al., 2008).

The PATH study, in individuals in their early 60s, demonstrates that these effects can be found concurrently in the same population. On average individuals with T2D had 2% lower total brain volume, and 1% lower total grey matter volume, 3% lower white matter volume (Walsh et al., 2017), significantly thinner cortices (mean thickness 2.27 mm vs NFG 2.32 mm), but experienced a slower rate of subsequent atrophy over twelve years (annualised percentage atrophy 0.33% vs NFG −0.38) (Shaw et al., 2017). Further, focussing on sub-structures, participants with T2D also had a 5% smaller thalamus, 12 smaller corpus callosum (Walsh et al., 2019); differently shaped hippocampi, caudate, putamen and globus pallidus, with voxel-wise shape comparison broadly indicating inward deformations consistent with volumetric differences (Zhang et al., 2016).

A greater number of studies investigated associations between white matter lesions or lacunar infarcts and T2D. However, there was a high heterogeneity in the type of populations studied (vascular, general, out-patients) and in the type of measures considered. Overall, the evidence was stronger for lacunar infarcts with T2D being associated with 30–130% increased risk of presence of lacunar infarcts (van Harten et al., 2006).

In addition, the systematic review (van Harten et al., 2006) discussed above suggests that a greater number of studies investigating associations between white matter lesions or lacunar infarcts and T2D are available than for cerebral atrophy. However, it also points to substantial heterogeneity between studies in the type of populations investigated (vascular, general, out-patients) and in the type of measures considered. Overall, the evidence appears stronger for lacunar infarcts than for brain atrophy with T2D being associated with 30–130% increased risk of lacunar infarcts (van Harten et al., 2006). Although these associations appear more prevalent for symptomatic than for asymptomatic lacunar infarcts. In the PATH study, T2D was not associated with a greater prevalence of white matter lesions (white matter hyper-intensities) observed on T1-weighted MRI scans at baseline (age 60–64 years) (Kumar et al., 2008).

7.2.2. Fasting blood glucose

Consistent with the above findings, higher fasting blood glucose levels have also been found to be associated with lower grey matter volume in T2D. For example, Bryan et al. reported that every additional 10 mg/dl in FBG (0.56 mmol/l; n = 614) was associated with a 0.5% decrease in grey matter volume (Bryan et al., 2014). Similarly, Tiehuis et al. reported that total brain volume was negatively associated with both FBG levels (0.12% per mmol/L; 2.16% per mg/dl) and disease duration (0.05% per year) in T2D patients (n = 151, 61.5 years) (Tiehuis et al., 2008). In addition, Weinstein et al. found, in a relatively young cohort (n = 1597, 40.3 years), that FBG levels were negatively associated with regional grey matter volumes (independently of the effect of T2D which was only 2.1% in this sample) in the occipital and temporal lobes as well as with larger white matter hyperintensities volume, and lower white matter integrity (FA) (Weinstein et al., 2015). Consistent results were also reported in a large Japanese cross-sectional study (n = 1151, 62.6 years), in which elevated FBG was associated with an 86% increased risk of silent brain lesions (greater than3mm) and a 153% increased risk of *peri*-ventricular white matter hyperintensities (Bokura et al., 2008). Critically, recent evidence from a clinical trial contrasting standard vs intensive glycemic treatment showed that those who were more aggressively treated experienced lower grey matter atrophy over a 40-month follow-up (Erus et al.,

2015). These findings appear to support the view that a substantial part of the brain atrophy detected in T2D is due to high glucose levels rather than other aspects of the pathophysiology of the disease.

However, very few studies have investigated the question of whether variability in FBG levels within the normal range is associated with brain structure. Using data from the PATH study, we were the first to systematically investigate such an association in a large cohort of community-living individuals. Indeed, we found that in individuals without diabetes (n = 249, 62.6 years) higher normal FBG was associated with greater hippocampal and amygdalar atrophy and explained 6–10% in volume change over 4 years (Cherbuin et al., 2012). Moreover, follow-up investigations on the same sample showed consistent associations in other brain regions. At first assessment, higher FBG was associated with striatal differences particularly in the caudate and putamen (Zhang et al., 2016). In addition, longitudinal analyses confirmed this association but more so in those with T2D. Moreover, at second assessment when participants were aged 68–73 years, FBG at the high end of the accepted normal range was also associated with lower regional brain volume in the middle and inferior frontal gyri (Mortby et al., 2013). Analyses over 12 years of follow-up indicated that an increase of 1 mmol/l (18 mg/dl) in FBG above 5 mmol/l (90 mg/dl) was associated with a 10–13% increased rate of cortical thinning in the insula, as well as posterior cingulate, parahippocampal and medial orbitofrontal cortex (Shaw et al., 2017). Concurrently, an association between glucose and total brain atrophy was also detected with each additional 1 mmol/l (18 mg/dl) being associated with approximately half a millilitre additional atrophy per year (0.14%/mmol/l/year or 2.5%/mg/dl/year) (Walsh et al., 2018). In a more recent exploration, when T2D status, demographic, and lifestyle factors were controlled for, we found each 1 mmol/l (18 mg/dl) of glucose was consistently, but not significantly (likely due to shared variance with BMI), associated with lower brain volumes (1.314 ml lower total brain volume, 1.516 ml lower grey matter volume, 0.030 ml lower thalamus volume, 0.034 ml lower white matter volume and 0.012 ml corpus callosum volume) (Walsh et al., 2019).

7.3. Metabolic and functional brain changes

7.3.1. T2D

T2D is associated with decreased blood flow and increased cerebrovascular resistance (Pruzin et al., 2018; Novak et al., 2006). This contributes to a higher prevalence of small vessel disease, deep white matter lesions, infarcts, atherosclerosis and related pathology in T2D than NFG (Nelson et al., 2009; Ryan et al., 2014; Biessels and Reijmer, 2014). It follows that T2D is also associated with greater damage and poorer neurovascular recovery following neurological insults such as stroke in animals (Zhang et al., 2016) and humans (both children aged 16 or less (Michaud et al., 1991), and adults (Pruzin et al., 2018; He et al., 2017). PET studies indicate that insulin resistance in T2D is associated with impaired cerebral glucose metabolic rate, especially in the parietal and prefrontal cortices (Baker et al., 2011), and that this is linked to amyloid deposition in these same areas (Willette et al., 2015).

7.3.2. Fasting blood glucose

Animal models demonstrate a link between glucose phosphorylation and cerebral blood flow. Acute changes to FBG induced by fasting can increase cerebral blood flow, particularly in the cortex and cerebellum (Cremer et al., 1983). In humans, cerebral bloodflow in individuals with IFG has been found to decrease at a significantly faster rate than in NFG in some regions (frontal, parietal, and temporal cortices), while it increases at a significantly faster rate in others (frontal, temporal, and precentral gyri) (Thambisetty et al., 2013). The link between high FBG and stroke prognosis is confounded by stress-induced hyperglycemia that can be induced by the strokes, though FBG of 6.1 mmol/L (110 mg/dl) and over at the time of hospital admission in individuals without diabetes has been associated with higher mortality and poorer functional recovery following ischemic stroke (Capes et al., 2001). Similarly to T2D, there is PET evidence that insulin resistance in NFG and IFG is associated with lower cerebral glucose metabolism across large portions of the frontal, lateral parietal, lateral temporal, and medial temporal lobes (Willette et al., 2015).

8. T2D risk factors

8.1. Diet

There is good evidence in the animal and human literature indicating that diet energy content and quality are associated with both glucose metabolism and cerebral structure. Animal studies have shown that diets lower in energy content and/or of higher quality (mostly lower in fat and sugar) are associated with larger brain volumes, better white matter integrity, and better cerebral health (Kanoski et al., 2010; Casadesus et al., 2002; Titova et al., 2013). The human literature is more sparse, and less consistent. The Mediterranean-style diet has received most attention and while some studies have found positive cross-sectional associations between higher adherence to the Mediterranean diet and larger brain volumes (van Harten et al., 2006; Gu et al., 2015), cortical thickness (Staubo et al., 2017), cerebral connectivity (Pelletier et al., 2015), or fewer white matter lesions (Scarmeas et al., 2011; Gardener et al., 2012), other studies failed to replicate these findings (Luciano et al., 2017). Only one study reporting longitudinal associations has been identified. Luciano et al. showed in a large neuroimaging sample (n = 398, 70 years) that higher Mediterranean diet adherence was associated with less brain shrinkage over 3 years (Luciano et al., 2017). In addition, some evidence indicating that higher meat, carbohydrate and sugars and lower fish and vegetables intake is associated with lower brain volumes (Gu et al., 2015) and cortical thickness (Staubo et al., 2017).

8.2. Obesity

Because obesity and T2D are highly co-morbid and rely on overlapping mechanisms, such as leptin deficiency and insulin insensitivity (e.g. ob/ob mouse and Zucker obese rat models (Cefalu, 2006)), there is substantial overlap in animal models used to explore the impact of T2D and obesity on the brain. Some evidence which distinguishes the impact of obesity from that of T2D comes from a small literature exploring the impact of obesity acutely induced by overfeeding. Overfeeding-induced obesity has been associated with decreased blood flow in the prefrontal cortices in minipigs (Val-Laillet et al., 2011), depression-like upregulation of pCREB in the striatum and hypothalamic dysfunction (Sharma and Fulton, 2013) and deficits in leptin sensitivity in the arcuate nucleus in mice (Münzberg et al., 2004). Obesity following high-fat diets in particular were linked with chronic inflammation and impaired cognition in mice (Pistell et al., 2010).

The evidence linking adiposity/obesity to brain structure in humans is somewhat limited, mostly cross-sectional, and based on heterogeneous adiposity measures. However, a recent review concluded that higher adiposity may be associated with frontal lower gray matter volumes across all ages and lower parietal and temporal gray matter atrophy in middle- and old-age, while the white matter appears to be largely spared (Willette and Kapogiannis, 2015). Notably this occurs even in adolescence, with comorbid obesity and T2D associated with higher rates of cerebral atrophy, and reduced hippocampal and prefrontal cortex volumes (Bruehl et al., 2011). In the PATH study, we found that higher adiposity in older age was significantly associated with accelerated cortical atrophy, in particular thinning in the posterior cingulate cortex (n = 404, age = 40–44 (Shaw et al., 2017), and lower hippocampal volume (n = 266, age = 60–64 (Cherbuin et al., 2012). Further, we found a combination of high BMI and high blood glucose was particularly detrimental to total brain and thalamus volume (Walsh et al., 2019).

8.3. Exercise

The evidence linking physical activity with cerebral health is strong. In rodents, voluntary and forced exercise has been shown to be associated with angiogenesis (Swain et al., 2003), synaptogenesis and neurogenesis (primarily in the hippocampus, primarily involving BDNF and IGF-1) (Nokia et al., 2016; Van Praag et al., 1999; Redila and Christie, 2006; Voss et al., 2011), larger hippocampal volumes (Voss et al., 2013), smaller infarctions (Ang et al., 2003) and less oxidative damage and inflammation following ischemic stroke (Austin et al., 2014; Li et al., 2004). There is also evidence that exercise is protective against neurodegenerative conditions such as Parkinson's disease (Smith and Zigmond, 2003), and the neuropathology and cognitive indicators of Dementia (Tapia-Rojas et al., 2016; Ahlskog et al., 2011). These beneficial effects are linked to reduced inflammation (Ryan and Nolan, 2016) and higher BDNF levels (Bechara and Kelly, 2013; Ang et al., 2003) and related neurogenesis and energy homeostasis (Marosi and Mattson, 2014; Vaynman et al., 2006).

Consistent findings have been demonstrated in humans (Voss et al., 2013). Direct observation of synaptogenesis in humans due to exercise is difficult to obtain, but its occurrence is supported by convergent evidence of exercise-related upregulation of neurotrophic factors measured peripherally (Voss et al., 2011; Vega et al., 2006; Nybo et al., 2002), increased gene expression associated with neuroplasticity (Cotman and Berchtold, 2002), and improved prognosis following ischemic stroke (Gordon et al., 2004). Multiple studies note a positive association between physical exercise and cortical thickness (Rogge et al., 2018), larger grey and white matter volume, particularly in the prefrontal cortex (Voss et al., 2011; Colcombe et al., 2006) and hippocampus (Erickson et al., 2011; Kleemeyer et al., 2016). The positive association between physical exercise and brain volume is more pronounced in older adults, suggesting it plays a role in slowing age-associated atrophy (Colcombe et al., 2006), and can be helpful in preserving function in cases of neurodegenerative disease such as dementia (Heyn et al., 2004). The major pathways mediating the beneficial effects of exercise on the brain are through managing other risk factors such as adiposity, T2D, and atherosclerosis (Ahlskog et al., 2011; Stults-Kolehmainen, 2013; Heyn et al., 2004), release of neurotrophins (Voss et al., 2013) and reduction of neural inflammation (Ryan and Nolan, 2016), and promoting blood flow via cardiorespiratory fitness (Rogge et al., 2018; Burns et al., 2008).

8.4. Section summary

Together these findings suggest that widespread brain atrophy and white matter lesions are more prevalent in T2D and that increased FBG is associated with higher atrophy not only in T2D but also in normal older adults with higher FBG levels within the normal range. Importantly, these effects appear to start developing and be detectable in middle-age, before 60 years, and increase with disease duration.

9. Blood glucose and cognition

9.1. T2d

In animal models, T2D typically induced through a high fat diet and/or by injection of streptozotocin leading to a sustained increase in blood glucose and body weight has been linked to poorer episodic, working, and spatial memory (object recognition, Morris maze, and Y maze tasks) (Noor and Zahid, 2017; Carvalho et al., 2013), and learning (lever-press task) (Moreira et al., 2007). Several studies note that the neurocognitive deficits seen in these T2D animal models mirror those seen in dementia (Carvalho et al., 2013).

In humans strong and consistent evidence shows that T2D is associated with an increased risk of cognitive decline and dementia. A recent *meta*-analysis (Adams, 2013) summarising findings from 14 studies and more than 2 million individuals demonstrates that T2D is associated with 60% increased risk of dementia. Interestingly, this effect is overall somewhat greater (4%) in women than men, and stronger for vascular (women: RR 2.34; men: RR 1.73) than for non-vascular dementia (women: RR 1.53; men: RR 1.49). Another large *meta*-analysis also indicates that a higher risk of AD is associated with T2D according to ethnicity (Western: RR 1.36; Eastern: RR 1.53) (Zhang et al., 2017). Moreover, a previous *meta*-analysis found that T2D was associated with a 20% increased risk of Mild Cognitive Impairment (MCI), the preclinical stage to dementia (Cheng et al., 2012).

Of critical importance is that T2D does not only have a distal risk for cognitive function (i.e. for dementia) but is linked to impairment along the disease process with symptoms being present before or developing soon after clinical diagnosis. Meta-analyses of the available literature show that T2D is associated with lower performance in motor function, episodic and logical memory, verbal fluency, cognitive flexibility, attention and processing speed (Monette et al., 2014; Sadanand et al., 2016; Palta et al., 2014). This is also observed in the PATH data, where we found that T2D was associated with significantly poorer performance on a measure of fine motor dexterity (the Purdue pegboard test (Zhang et al., 2018), alongside higher total brain atrophy (n = 478, age 60–64 (Kumar et al., 2008), and lower striatal volume (n = 271, age 60–64 (Zhang et al., 2016). Importantly, in the same cohort T2D was also associated with an increased risk of developing mild cognitive disorders (Cherbuin et al., 2009).

9.2. Fasting blood glucose

In addition to the cognitive impairments associated with T2D as a whole it has also been shown that amongst individuals with T2D those with higher FBG experience faster cognitive decline and are at higher risk of dementia. But perhaps of greater significance, this effect does not appear to be restricted to T2D but is also detectable in its pre-clinical stages (IFG and IR), and within the normal FBG range in people without T2D. For example, in a cohort of older Japanese individuals without T2D (n = 1017, 68.5 years), higher glucose levels (6.1–6.9 mmol/l) 2 h after a glucose tolerance test compared to normal levels (< 5.6 mmol/l) have been found to be associated with a higher risk of vascular dementia (HR 1.93, 95% CI 1.03–3.61) but not AD or other dementias (Ohara et al., 2011). In children, there is some evidence that blood glucose is implicated in self-control (Gailliot and Baumeister, 2007), though this is contentious (Vadillo et al., 2012). More persuasively, in a cohort of adults without T2D (n = 41, 64.7 years) higher FBG within the normal range (< 6.1 mmol/l) was associated with slower reaction time (Raizes et al., 2016) (each 1 mmol/l increase in plasma glucose associated with 0.05 s (2%) slower reaction time). In a third study of individuals without T2D (n = 411, 50.6 years) higher FBG was associated with poorer episodic memory in women but not in men (Rolandsson et al., 2008). Finally, in a large longitudinal study (n = 838; 63.1 years; 3.3% individuals with T2D), higher FBG was associated with greater decline in general cognition (each 1 mmol/L higher FBG = 9% greater decline per year), perceptual speed (each 1 mmol/L ≈ 7% greater decline/year), verbal (each 1 mmol/L ≈ 3% greater decline/year) and spatial abilities (each 1 mmol/L ≈ 6% greater decline/year) (Seetharaman et al., 2015). Overall, these findings suggest a consistent association between FBG in the high end of the accepted normal range and lower cognitive function in mid-life to early old age in individuals free of T2D. Unfortunately, to date no *meta*-analysis has been conducted to more clearly characterise the association between FBG levels within the normal range and cognitive function in people free of T2D and therefore caution should be exercised in interpreting these findings. In the older PATH cohort (age 60–65 years), blood glucose levels in people without T2D were associated with lower regional volumes (grey and white matter) and corresponding cognitive deficits similar to the patterns found in the literature, notably higher FBG (6.1 mmol/L and higher) being associated with lower frontal gyri

volumes and performance on working memory and reaction time tasks (Mortby et al., 2013).

9.3. Risk factors

9.3.1. Obesity

A clear link has been demonstrated between mid-life obesity and the risk of cognitive impairment later in life with individuals with obesity being at a 60–100% increased risk of dementia (Loef and Walach, 2013; Anstey et al., 2011). Moreover, a recent systematic review (Prickett et al., 2015) investigating the association between obesity and cognitive function and including 17 studies surveying individuals below the age of 65 has found that mid-life obesity was associated with lower performance in cognitive functioning, psychomotor performance and speed, visual construction, concept formation and set shifting, and decision making (but was inconclusive for visual memory, verbal memory, complex attention, delay discounting and inhibition). Importantly, this effect does not seem to be limited to mid-life obesity or late life cognition. For example, a cross-sectional study of 299 women (18–35 years) found that being obese was associated with significantly lower attention scores (Cook, 2017). Moreover, a *meta*-analysis of weight loss interventions in individuals with obese/overweight across twenty studies, 13 of which were longitudinal, found that weight loss was associated with a significant improvement in attention and memory (Veronese et al., 2016). Similar finding were also demonstrated across bariatric surgery randomised controlled trials (Thiara et al., 2017).

9.3.2. Exercise

The evidence linking physical activity and cognitive decline is strong. Findings from systematic reviews indicate that participating in regular exercise is associated with a 15–40% decreased risk of dementia (Beckett et al., 2015). As for obesity, the protective effect of exercise is already detectable in relation to general cognition in non-demented individuals. Our recent *meta*-analysis (Northey et al., 2018) of exercise interventions in people over 50 years shows that regular exercise (45–60 min 2–7 days per week) at moderate to high intensity is associated with improved cognitive function across all domains tested (global, attention, executive, memory, working memory). In PATH, physical activity was found to be positively associated with cognitive performance across multiple domains, particularly in the youngest cohort (aged 20–25), a stable, longitudinal association (Bielak et al., 2014).

9.3.3. Diet

Caloric overconsumption has been associated with deficits in global cognition, executive function, attention, information processing, and in particular memory (Reichelt et al., 2018; Roberts et al., 2012; Attuquayefio and Stevenson, 2015), while caloric restriction has been associated with preserved cognition and enhanced memory (Murphy et al., 2014). Although evidence for other macronutrients such as protein and carbohydrate is mixed (Attuquayefio and Stevenson, 2015), it is well established that diets high in fat, particularly in tandem with caloric overconsumption, are detrimental to cognitive health (Attuquayefio and Stevenson, 2015; Solfrizzi et al., 2017). Micronutrients, chiefly vitamins (notably B, C, and folate) (Solfrizzi et al., 2017; Travica et al., 2017), flavonoids (Williams and Spencer, 2012), antioxidants (particularly polyphenols (Solfrizzi et al., 2017) such as resveratrol (Murphy et al., 2014), curcumin (Kuszewski et al., 2018) and caffeine (Panza et al., 2015), and long chain polyunsaturated fatty acids (particularly omega-3 (Murphy et al., 2014; Cutuli et al., 2016) have been shown to benefit memory, semantic fluency, working memory, executive function, and reduce risk of developing cognitive impairment. However, it is likely these effects are driven, at least in part, by the detrimental impact of deficiencies, rather than surplus consumption providing benefits (Solfrizzi et al., 2017; Travica et al., 2017).

A dietary pattern perspective places macro- and micro-nutrient intake in the whole dietary context. An unhealthy, 'Western' dietary pattern, characterised by red meat, processed and fatty foods, has been associated with global cognitive, and specifically visuospatial, decline (Solfrizzi et al., 2017; Shakersain et al., 2016). Conversely, a 'Mediterranean' dietary pattern, characterised by legumes, fresh vegetables, grains, and monounsaturated fatty acids has been associated with superior cognitive function and reduced risk of cognitive decline and developing Alzheimer's disease (Feart et al., 2009; Lourida et al., 2013). This has led to the development of diets designed to improve cognition in ageing and reduce the risk of Alzheimer's disease, such as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet (Morris et al., 2015). The MIND diet has been associated with a 20% reduction in the likelihood of developing mild cognitive impairment in the PATH study (n = 1228, participants aged 72–76) (Hosking et al., 2017).

9.3.4. Section summary

High pre-clinical FBG and T2D both have a negative impact on cognitive function in ageing. This manifests in poorer performance and accelerated decline in measures of global cognition, more specifically memory, and increased risk of developing dementia. Risk factors for high FBG and T2D such as obesity, sedentary lifestyle, and poor diet are themselves directly implicated in cognitive decline.

10. Biological mechanisms mediating risk

While the findings reviewed above provides a strong evidence base linking increasing FBG and T2D to neurodegeneration and cognitive decline, most of the human research is correlational and therefore cannot address the question of causation. Although, causal links in humans cannot be unambiguously resolved for a complex pathology which takes years to develop and involves the interaction of several factors, one approach to clarifying causal links is the plausible identification of biological mechanisms that are likely to explain the pathophysiology of the disease under consideration. For this reason, this section will briefly review the main mechanisms which contribute the effect of FBG, T2D and their risk factors on cerebral and cognitive health.

10.1. Oxidative stress

Oxidative stress (OS) is one of the main mechanisms contributing to molecular and cellular senescence and it is also implicated in the neuropathology of T2D. OS is an umbrella term used to refer to the imbalance in production of reactive oxygen species (superoxide and hydrogen peroxide) as part of metabolic processes relative to the counteractive action of anti-oxidants that are mostly produced through protective cellular mechanisms but also contributed through dietary intake (Lugrin et al., 2014). OS is known to damage DNA, shorten telomeres (Reichert and Stier, 2017), and degrade cellular structure and thus is associated with increased apoptosis and impaired cellular function. In the CNS it is also associated with decreased synapto and neuro-genesis (Yuan et al., 2015), vascular damage (Forstermann, 2010), and increased protein mis-folding leading to increased amyloid plaques and tauopathy (Alavi Naini and Soussi-Yanicostas, 2015, 2015).

Increased OS has been shown to be increased in animal models of T2D and to be associated with neuro-vascular damage, glial proliferation and shrunken and damaged neuronal structures (Yang et al., 2013; Zherebitskaya et al., 2009). In humans, associations between increased OS levels in T2D have also been reported. There is limited evidence on the association between glucose levels and OS. However, at least in children with type 1 diabetes, fluctuation in blood glucose was found to be associated with higher OS levels even in those with stable glycaemia (Meng et al., 2015). Importantly, in vitro studies investigating

variability in glucose levels compared to hyperglycaemia have suggested that fluctuation in glucose levels may produce more OS and be more damaging than stably high glucose levels (Wright et al., 2006). However, whether high glucose levels lead to increased OS or whether a bi-directional relationship is at play is also under question since higher OS levels appear to be associated with insulin resistance and impaired glucose tolerance and pathological pathways linking OS to damage of insulin producing cells has also been identified (Kopprasch et al., 2015; Henriksen et al., 2011; Hurrle and Hsu, 2017).

10.2. Inflammation

Chronic inflammation plays a major role in the development of T2D. Adipose tissue produces pro-inflammatory cytokines and overweight and obesity have been demonstrated to lead to heightened low grade systemic inflammation (Hotamisligil, 2017; Reilly and Saltiel, 2017). Moreover, as physical activity has anti-inflammatory effects, the sedentary lifestyle typically associated with the development of T2D compounds the pro-inflammatory mechanisms associated with increased adiposity (Pedersen, 2017). Pro-inflammatory cascades are further activated through the effect of poor diet and increased oxidative stress discussed above as well as other co-morbid conditions including depression and cardio-vascular disease (Minihane et al., 2015).

10.3. Impaired vascular health

Evidence from a recent *meta*-analysis indicates that chronic hyperglycemia is associated with increased risk of cardio-vascular disease, coronary heart disease, stroke, and peripheral arterial disease (Zhang et al., 2012). A number of mechanisms are thought to contribute to these effects. The increased production of OS and activation of pro-inflammatory cascades associated with elevated glucose levels leads to endothelial dysfunction (Hamilton and Watts, 2013) and vascular damage (Zhang et al., 2012). Elevated glucose levels promote the production of proteins, called advanced glycation end products, which contribute to the formation of plaques, atherosclerosis, and ultimately decreased blood flow in all organs including the brain (Aguiar et al., 2014). These processes progressively lead to the development of small vessel disease, chronic cerebral hypoxia, and neuronal damage (Sims et al., 2014; Martinez Sosa and Smith, 1979).

10.4. Impaired neurogenesis

Neurogenesis, while not widespread in the adult human brain, contributes significantly to hippocampal function. Brain-Derived Neurotrophic Factor (BDNF) is a major modulator of neurogenesis with higher levels being associated with increased production and differentiation of granule cells in the hippocampus. Higher blood glucose levels have been shown to be associated with lower BDNF levels and decreased neurogenesis (Krabbe et al., 2007). Interestingly, experimentally increased BDNF levels have been shown to attenuate hyperglycemia in male rats which may partially explain the protective role of exercise and environmental enrichment in protecting against neurodegeneration in the context of metabolic disease (Meek et al., 2013).

10.5. CNS insulin & neuronal metabolism

Closely tied to glucose metabolism, and strongly associated with adiposity, insulin is directly implicated in cognitive performance and decline (Ott et al., 2012; Plum et al., 2005). Peripheral insulin crosses the blood–brain barrier (Pardridge et al., 1985) and acts upon widespread neural insulin receptors which are concentrated in the olfactory bulb, cerebellum, hypothalamus, and hippocampus (Plum et al., 2005). Central insulin is upstream of signalling cascades implicated in synaptic plasticity, synaptogenesis, and neurogenesis (Kleinridders et al., 2014), and as previously noted, can be protective against OS (Augustin et al., 2015). Insulin resistance impairs the uptake of glucose in neurons and compromises their function. There is both observational and experimental evidence showing that insulin and Insulin-like Growth Factor (notably IGF-1 and IGF-2) can decrease the intracellular hallmarks of AD (circulating amyloid-β and hyperphosphorylated tau (Plum et al., 2005), although the causal association between chronic insulin resistance and the development of AD remains unclear (Freiherr et al., 2013). In both healthy and cognitively declining individuals, insulin resistance can cause widespread dysfunction most clearly seen in the hippocampus, and consequently memory function (Plum et al., 2005; Convit, 2005). This has therapeutic potential - intranasal administration of insulin is associated with acute and prologued improvements in memory, and is therefore being pursued as a possible AD treatment (Ott et al., 2012; Freiherr et al., 2013).

10.6. Protein mis-folding

Although protein mis-folding receives more attention in acute conditions such as Alzheimer's (amyloid plaque) and Parkinson's (Lewy bodies) disease it is a key ageing mechanism throughout the body and in the brain (Basaiawmoit and Rattan, 2010). Increasing age and tissue damage mediated by the processes discussed above are associated with impaired clearance of the bi-products of cellular metabolism. The accumulation of these bi-products progressively compromises cellular function and leads to further damage and increasing aggregation of mis-folded proteins thus further impacting function.

The patho-physiology of T2D contributes to the accumulation of mis-folded proteins in several ways. Raised OS and pro-inflammatory activity associated with the development of T2D contribute to damage of cellular mechanisms which become less efficient at clearing mis-folded proteins or in repairing DNA damage associated with protein mis-folding. Moreover, cerebro-vascular disease is associated with decreased clearance of mis-folded proteins, at least in Alzheimer's and Parkinson's disease, and thus leads to increased amyloid plaque and Lewy bodies formation (Yarchoan et al., 2012; Grimmer et al., 2012; Choi et al., 2011; van der Holst et al., 2015; Deleidi and Maetzler, 2012).

10.7. Section summary

Several concurrent biological mechanisms are associated with the patho-physiology of high blood glucose levels and T2D. Cellular damage and impaired neural function arising from an overabundance of reactive oxygen species, a situation known as oxidative stress, is associated bi-directionally with hyperglycaemia and T2D. Chronic inflammation promoted by excess adiopose tissue, lack of physical activity and poor diet further exacerbates oxidative stress and tissue damage. Hyperglycaemia and pro-inflammatory processes also contribute to vascular disease and have been linked with lower Brain-Derived Neurotrophic Factor levels, thus compromising neuronal integrity and impairing neurogenesis. Disruption of central insulin function associated with T2D leads to impaired energy metabolism in neurons and is implicated in declining cognitive performance. There is also growing evidence that T2D is implicated in protein mis-folding, largely via oxidative stress and inflammation, and thus contributes to the development of neurodegenerative disease such as Alzheimer's.

11. Conclusions

The notion that T2D is associated with neurodegeneration, cognitive impairment, dementia and mortality is not new. However, these associations are often thought to be mostly relevant in old age despite the availability of substantial evidence indicating that the pathological processes at play are initiated in mid-adulthood or before. The aim of this review was therefore to comprehensively summarise the available

research literature demonstrating a link between the early emergence and impact of the main risk factors for T2D (obesity, physical activity, and dietary intake), their associations with increasing FBG levels with ageing and the progressive dysregulation of glucose metabolism, and the impact these effects have on cerebral health and cognitive function before, during and after the clinical development of T2D. In addition, a particular focus was on evaluating whether higher fasting blood glucose levels within what is considered the normal range present a risk to brain and cognitive health.

As a whole the body of evidence presented above strongly suggests that persistently elevated FBG are associated with brain shrinkage, progressive loss of function across several cognitive domains, the development of dementia, and ultimately, premature death. It is also clear that T2D's main risk factors contribute in a major way to these effects and that clinical T2D represents the greatest risk to cerebral health. However, while their contributions overlap, each of these components appear to contribute separately and independently of each other to the neurodegenerative processes leading to functional loss. Of major importance is the fact that clear pathological mechanisms supporting a causal link between glucose metabolism dysregulation and neurodegeneration have been identified.

It is of particular concern that the pathological cascade leading to higher FBG and ultimately T2D typically begins decades before and starts impacting cerebral health and cognition from its onset. The implication of these findings is that policy responses and interventions aimed at preserving neurocognitive capital and slowing cognitive decline in ageing should be initiated as early as possible and preferably in childhood or early adulthood and be sustained across the adult lifespan.

Disclosure

The authors have reported no conflicts of interest. This study is NOT industry sponsored.

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Declaration of Competing Interest

None.

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